TRANSACTIONS

OF THE

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

VOLUME XXXV

TRANSACTIONS

OF THE

AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

Fifty-fourth Annual Meeting held at
Hershey, Pennsylvania

May 27, 28 and 29, 1942

Volume XXXV

[illegible]

Published for the Association by
The Bruce Publishing Company
Saint Paul and Minneapolis
1943

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THE AMERICAN ASSOCIATION OF GENITO-URINARY SURGEONS

FIRST DAY, MAY 27, 1942

TOXIC RENAL REACTIONS FOLLOWING THE USE OF SULFADIAZINE

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From the Urological Service of Bellevue Hospital, New York City

Therapeutic enthusiasm in the use of the sulfonamide preparations has often been tempered by the accompaniment of a disturbingly high incidence of toxic reactions and calculous formation in the urinary tract, with and without anuria. The search for a drug that would not result in serious sequelæ has led to the synthesis of 2 sulfanilamido-pyrimidine, or sulfadiazine by Roblin, Williams, Winnek and English. Pharmacologic investigation has demonstrated the readiness with which the free form of sulfadiazine is concentrated in the blood, the comparatively slow excretion, and the comparatively greater solubility of the acetyl-derivative in the urine. It is believed by many workers, especially Flippin and Plummer, that sulfadiazine will replace sulfathiazole and sulfapyridine. Certainly, today, it is regarded by many physicians as quite innocuous, and chiefly for that reason is considered the ideal drug of the sulfonamide group.

To show that the employment of this drug is not without danger is the primary purpose of this paper. It is our opinion that sulfadiazine, like its relatives having the radical of the parent compound, may under certain circumstances cause toxic reactions, and that such reactions occasionally are so severe that one is forced to question the propriety of statements which have appeared in the literature alleging the absence of dangerous sequelæ which have occurred after the employment of other sulfonamides.

Employing the albino rat, Lehr and Antopol have recently investigated the toxicity of sulfadiazine and acetyl-sulfadiazine with especial reference to renal lesions. They found a strikingly high incidence of kidney damage after the injection of fatal doses of sodium sulfadiazine, which they explained as due to the poor solubility of the free drug which may be precipitated in the renal

convoluted tubules. Because of the poor solubility of sulfadiazine, obstruction of the kidney by the precipitation of this compound may be of long duration, and lead to a severe calcifying nephrosis. Their findings indicate that the tendency for the retention of the free sulfadiazine in the circulation increases with impairment of renal function and they do not suggest that kidney damage will be less likely to occur from the use of sulfadiazine than from the other sulfonamides as hitherto reported.

The more recent clinical reviews of sulfadiazine in pneumonia have shown a greater frequency of the toxic renal effects than was at first reported. Billings and Wood treated 105 patients suffering from pneumococcus pneumonia with sulfadiazine, and found a frequent occurrence of crystals of the acetylated form. Finland reviewed 116 cases and found crystals in thirty-five (7.8 per cent), a rise of non-protein nitrogen in five (1.1 per cent), hematuria in three (0.7 per cent), and anuria in one patient (0.2 per cent). Flippin, in a series of 200 cases of pneumonia, found nine cases (4 per cent) of hematuria. Dowling reported 116 cases with an elevation of non-protein nitrogen in two (1.5 per cent). The literature today contains reports on well over 1,200 patients treated with sulfadiazine. Thus far there have been no deaths ascribed to its use, and there have been only two instances of anuria, one reported by Finland, and one by Thompson; both patients recovered completely. In these two cases, the anuria was shown to be due to ureteral block by the sulfadiazine crystals.*

During the past six months at Bellevue Hospital (approximately September, 1941, to February, 1942, inclusive), sulfadiazine has had an extensive use, supplanting sulfathiazole in the treatment of pneumonia. The clinical results have been in large measure excellent, but the urological service has been called into frequent consultation because of the complications which have followed its administration. We have observed over thirty-five patients in whom the crystals of acetyl-sulfadiazine were found in the urine, but apart from an occasional mild colic and microscopic hematuria these patients soon recovered completely. It should be remembered, however, that crystals are of no particular signifi-

*Since the preliminary report of these cases was presented on March 18, 1942, at the New York Academy of Medicine (Section of Genito-Urinary Surgery), several deaths following the use of sulfadiazine have been reported. Notable among such cases are those by the following authors: Bradford and Shaffer, Hellwig and Reed, Rottino and La Rotonda.

cance except in freshly voided warm urine. We have been more concerned over ten patients (seen in consultation by the urologic service) all of whom developed severe toxic reactions following the use of the drug. Seven of these patients recovered; three died.

There are four medical and four surgical divisions in Bellevue Hospital. All of the patients reported in the following cases, except one, were admitted to one or another of the medical services. The exception (Case 8) was admitted to a surgical service.

Case 1.—An eighty-year-old negress was admitted to the medical service because of marked vomiting and non-bloody diarrhea, accompanied by chills and fever of two days' duration. Physical examination showed she was acutely ill, toxic, with a temperature of 100, and pulse 130. There was evidence of a right lower lobe pneumonia and a probable chronic cholecystitis. A catheterized urine specimen revealed albumin ++, pus ++, specific gravity 1.017. The non-protein nitrogen was 36 mg.

She was placed on sulfadiazine gm. 2 by mouth, followed by gm. 1 q. 4 h. day and night. Her fluid intake the first few days was kept well over 2,000 c.c., but thereafter no adequate measurement was maintained. On the twenty-first day of treatment, it was noted that she was putting out almost no urine. At this time (non-protein nitrogen 46 and the sulfadiazine blood level 32.2) she passed a small concretion composed of acetyl-sulfadiazine. She had received in all 128 gm. of sulfadiazine. It was planned to make a cystoscopic examination of this patient but she died before it could be accomplished. Autopsy revealed the following: Right kidney: Acute pyelitis. Much fine yellowish sand in kidney pelvis and ureter which was much dilated. Left kidney: Similar to right but was less inflamed and contained no sand. Left ureter also dilated but contained no sand. There were no crystals in the tubules of either kidney. The bladder contained crystalline deposits similar to those in the right kidney pelvis and ureter.

Case 2.—A sixty-eight-year-old negress was admitted with a one-week history of severe cough, profuse blood-tinged sputum, chills and pain in the left chest. Physical examination revealed an acutely ill, dyspneic female. The findings were those of a very toxic lobar pneumonia (Type II) involving the left lower lobe. The non-protein nitrogen was 36. The patient was put on sulfadiazine therapy, at first 2 gm. of the drug orally, followed by 1 gm. q. 4 h. After 10 gm. of the drug had been given by mouth, she appeared to be very toxic because of her pneumonia, so that 2.5 gm. of sodium sulfadiazine was given intravenously. She took fluids very poorly, and was given a clysis of 2,000 c.c. of 5 per cent glucose saline each day, but her urinary output continued to be exceedingly poor. Catheterization after 5 gm. of the drug had been given yielded 30 c.c. and after

the intravenous dose yielded no urine. She had received in all 12.5 gm. of the drug, and her non-protein nitrogen was 80. A blood level was 20.1. After consultation, cystoscopy was immediately done. No urine was found in the bladder. Both catheters were introduced to the renal pelves; there was no obstruction to the catheters, and no urine was seen to drip from the catheters. These were left in place and frequently irrigated. There was no urinary output. During the next twelve hours, the patient developed edema and died. Autopsy revealed the following: In addition to parenchymatous degeneration and possible acute nephrosis, there were blood clots in the pelves and calyces of both kidneys. In the upper pole of each kidney was a fairly large solitary cyst. There were hemorrhages in the mucosa of both ureters and small blood clots in the left ureter. There was no evidence of crystals in kidney tubules, pelves or ureters.

Case 3.—A forty-eight-year-old woman was admitted with a two-week history of acute dyspnea and orthopnea. Physical examination revealed a pale female, markedly obese, dyspneic, and wheezing. The temperature was 102, respirations 44, pulse 100. The signs were those of acute congestive failure, and left lobar pneumonia, involving the lower two-thirds of the lung (Type II). She was immediately put on sulfathiazole gm. 4 by mouth, followed by gm. 1 q. 4 h. Because of the development of an empyema of the chest, following six days of this treatment, the sulfathiazole was discontinued, 32 gm. having been given. A chest tap was done after which sulfadiazine was given (initial dose of 2 gm. followed by 1 gm. every four hours). At this time her daily fluid intake was approximately 2,000 c.c. and the output about 1,000 c.c. She received 24 gm. of sulfadiazine for seven days when it was noted her output of urine was 100 c.c. in twenty-four hours. She was very drowsy. The blood level of sulfadiazine was 15.2 and the non-protein nitrogen 64. The urine contained pus (+), red blood cells +++ and innumerable crystals of acetyl-sulfadiazine. Cystoscopy was performed. No bladder urine was found on the introduction of the cystoscope. Many crystals of acetyl-sulfadiazine were found on the floor of the bladder. Catheters were introduced to the kidney pelves on both sides without apparent obstruction in either ureter. However, urine dripped from both catheters at once and without cessation for several minutes. The specimens thus obtained were loaded with crystals. The catheters were kept *in situ* and irrigated frequently with warm distilled water. Fluids were given intravenously. During the next few hours the urinary output rose to 320 c.c. and the non-protein nitrogen dropped to 40. Despite these favorable signs, the patient soon lapsed into a coma and died four days after the cystoscopic examination. Permission for an autopsy was refused.

Case 4.—A fifty-six-year-old white man was admitted, complaining of severe frontal headache, cough, malaise, and weakness of six days' duration. Physical examination revealed him to be acutely ill with temperature 103.6; the physical findings were those of a right lower lobe

pneumonia (Type XXIV). The urine was negative, and the non-protein nitrogen was 34. He was put on sulfadiazine therapy, being given 2 gm. orally at the start, followed by gm. 1 q. 4 h. His fluid intake averaged about 2,000 c.c. per day, and on the third post-admission day, after a total of 18 gm. of the drug had been given, he complained of marked dysuria, with pain in the right lower quadrant. His urine at this time was loaded with red cells and acetyl-sulfadiazine crystals. The drug was immediately discontinued and he was given an intravenous infusion. The sulfadiazine level was 10.5 mg. By the next morning, he appeared to be very drowsy, and catheterization yielded no urine. A sulfadiazine level at this time was 14.5 mg. Following urologic consultation, cystoscopy was done. No urine was found in the bladder. There were many crystals on the floor of the bladder which were later shown to be those of acetyl-sulfadiazine. A calculus in the left ureteral orifice was pushed out with a No. 5F. catheter which was then passed to the renal pelvis. A No. 5F. catheter was easily passed to the right renal pelvis. There was a cloudy continuous drip from each catheter. Both specimens showed pus and many acetyl-sulfadiazine crystals. The catheters were left *in situ* and irrigated every hour with warm distilled water. Fluids were given up to a daily intake of 4,000 c.c. The urinary output rose gradually, so that three days after cystoscopy, it reached 3,150 c.c. Following the removal of his catheter, the patient urinated readily and had no further difficulty.

Case 5.—A seventy-year-old white man was admitted with a two-day history of pain in his left chest and a fairly severe cough which produced a moderate amount of sputum. Physical examination revealed an acutely ill white male, with definite evidence of a left lower lobe pneumonia. The temperature was 104, the pulse 100. There was a definite trace of albumin in the urine. The non-protein nitrogen was 34. The patient was immediately given sulfadiazine gm. 4 at first, followed by gm. 1 q. 4 h. He was also given a daily intravenous infusion of 2,000 c.c. of 5 per cent glucose in saline solution so that his fluid intake was always over 3,000 c.c. On the ninth post-admission-day (52 gm. of the drug had been given), it was noted that he had not urinated for twenty-four hours and catheterization yielded no urine. At this time, his non-protein nitrogen was 75, and the blood level was 21.0. He was immediately seen by a member of the urologic service and cystoscopy was done. In the mouth of the left ureteral orifice was a greyish-black calculus which was finally teased out, and a No. 4F catheter was then easily passed to the renal pelvis. Urine dripped continuously from the catheter. The right orifice was edematous and there was apparently an obstruction in the ureter about 4 cm. from the orifice. This was finally passed with a No. 5F catheter which was then introduced about 27 cm. in all. Urine dripped slowly from the catheter. A flat plate of the catheter *in situ* indicated a small calculus in the right ureter about 5 cm.

from the orifice. The ureteral calculus removed from the mouth of the left ureter and that finally recovered from the right ureter were shown by analysis to contain 94 per cent acetyl-sulfadiazine. The catheters were left in the ureters and irrigation carried out with warm distilled water. The patient was given daily intravenous fluids up to 3,000 c.c. so that the daily intake in all was well over 4,500 c.c. The output rose the first day to 500 c.c., then to 3,600 c.c. and the non-protein nitrogen dropped on the second post-cystoscopic day to 37 mg. He was then transferred back to the medical service because of persistent signs in the base of the left lung. He was again placed on sulfadiazine, being given gm. 2 for the initial dose, followed by gm. 1 q. 4 h. until 12 gm. had been given. His signs disappeared without incident and he was later sent home.

Case 6.—A sixty-two-year-old Jewish man was admitted with a one-week history of cough and blackish sputum, associated with right-sided chest pain. He was acutely ill, confused, with a temperature of 104, pulse 104, respirations 32. There was physical evidence of a right upper lobe pneumonia. The urine analysis showed a fairly heavy cloud of albumin. The non-protein nitrogen was 82, and the sputum typing that of Type II. Because of a delirious state he was put in an oxygen tent and given intravenously 2.5 gm. of sodium sulfadiazine in distilled water plus 1,000 c.c. of glucose saline every four hours for three doses, after which he was put on gm. 1 q. 4 h. After four days of treatment, the non-protein nitrogen was 90 and many crystals were found in the urine. At this time he had received 20 gm. of the drug and the level was reported as 23.2. The drug was then reduced to gm. 1 t.i.d., and two days later he appeared markedly drowsy. Non-protein nitrogen was 180, and a blood level 21.0. The urinary output was 600 c.c. He was seen by a member of the urologic service. Intravenous fluids were advised. He received 4,000 c.c. daily. Almost immediately, the urinary output rose, so that the first day after the drug was stopped and treatment instituted, his output was 2,100. Six days later, the non-protein nitrogen was 29, the blood level 0.6. He was soon discharged, completely recovered.

Case 7.—A fifty-two-year-old woman was admitted to one of the medical services, complaining of pain in the right chest, moderate dyspnea and a productive cough. This was her second admission to this service. Physical examination revealed an acutely ill, dyspneic female—temperature 103, pulse 150, respirations 36. The physical findings were those of a lower lobe pneumonia, and arteriosclerotic heart disease, decompensated, with auricular fibrillation. She was immediately put on sulfadiazine, gm. 2 by mouth, followed by two more doses of gm. 2 at three-hour intervals. One gram of the drug was then given q. 4 h. The fluid intake remained in the neighborhood of 2,500 c.c. and the output 2,100 c.c. per day. Seven days after treatment was instituted, she complained of severe pain in the right

lower quadrant and had grossly bloody urine containing many crystals resembling those of acetyl-sulfadiazine. She had received a total of 33 gm. of the drug. A non-protein nitrogen at this time was 40 and the blood level 8.4. She was immediately seen by a member of the urologic staff and it was his opinion that because of a good urinary output, cystoscopy should be deferred, especially in view of her cardiac status. The drug was discontinued, her acid urine was

TABLE I. BRIEF RÉSUMÉ OF CLINICAL FINDINGS IN EACH CASE

Case	Sex	Age	Route of administration of drug	Total No. of days treated	Total dose of sulfadiazine in gm.	Fluid output in c.c. at time of unfavorable sequelae	Non-protein nitrogen	Blood level of sulfadiazine
1	F	80	Oral	21	128	800	35– 90	32.2
2	F	68	Oral & Intravenous	3	12	0	36– 82	22.2
3	F	48	Oral	7	24	100	36– 64	15.2
4	M	56	Oral	3	18	0	34– 40	14.5
5	M	70	Oral	9	52	0	34– 75	21.0
6	M	62	Oral & Intravenous	9	36.2	600	82–180	23.2
7	F	52	Oral	7	33	?	33– 40	8.4
8	F	93	Oral	3	22	?	?– 75	12.0
9	M	59	Oral	7	38	300	30– 60	18.4
10	M	62	Oral	8	36	100	33–140	27.2

alkalinized by giving sodium bicarbonate gm. 1 q. 4 h. Also daily infusions of 5 per cent glucose in saline solution up to 3,000 c.c. were given. Her hematuria disappeared on the fourth day after treatment was instituted, and she was discharged completely recovered.

Case 8.—A ninety-three-year-old woman was admitted to one of the surgical services with a history of having fallen off a chair, striking the right side of her thigh against the ground. There was immediate inability to use the right lower extremity. On admission, an x-ray examination confirmed the clinical impression of a fracture of the right femoral neck. The urine on admission was decidedly acid in reaction and otherwise negative. An open reduction was performed, the surgeon using a Hawley plate and fixing the fragments with a Smith-Peterson nail. Ten grams of sulfathiazole were poured into

TABLE II. (CONTINUATION OF TABLE I)

Case	Chief urinary sign of toxicity	Crystalline deposits in bladder	Evidence of crystals in ureters		Stones in ureters		Treatment by ureteral catheterization		Other method of treatment
			Right	Left	Right	Left	Right	Left	
1	Oliguria	+	+	+	—	—	+	+	Hypodermoclyses of saline and glucose
2	Anuria	+	+	+	—	—	+	+	Intravenous fluids
3	Anuria	+	+	+	—	—	+	+	Intravenous fluids
4	Anuria	+	+	+	—	+	+	+	Fluids, intravenous and by mouth
5	Anuria	—	—	—	+	+	+	+	Fluids intravenous and by mouth
6	Oliguria								Intravenous fluids
7	Hematuria								Intravenous fluids. Sodium bicarbonate by mouth
8	Hematuria								Intravenous fluids and Hartman's solution, also infusions of sodium lactate and sodium bicarbonate by mouth
9	Oliguria					+			Intravenous fluids
10	Oliguria	+	+	+				+	Intravenous fluids 5% glucose in distilled water alternating with Hartman's solution plus sodium lactate

Results	Urinary findings	Cystoscopic findings and treatment.
Died—Autopsy showed much fine yellowish sand in right pelvis and right ureter. Bladder contained crystalline deposits of similar nature.		
Died—Autopsy: Blood clots in pelves and calyces of both kidneys. Hemorrhages in mucosa of both ureters. Blood clots in left ureter. No crystalline deposits. Ureteral catheters left in situ and frequently irrigated with warm distilled water.		
Died—Ureteral catheters left in situ and frequently irrigated with warm distilled water.		
Recovered—Ureteral catheters left in situ and frequently irrigated with warm distilled water.		
Recovered—Ureteral catheters left in situ and frequently irrigated with warm distilled water.		
Recovered—No cystoscopy. Many crystals in urine.		
Recovered—No cystoscopy. Crystals resembling those of acetyl-sulfadiazine found in urine.		
Recovered—Recovered from the ill effects of the sulfadiazine but died about 2 months later as a result of the fracture. She was the oldest patient of the group—93.		
Recovered—X-ray indicated left ureteral calculus. Cystoscopy planned but not done because of severe depression following morphine injection. Stone passed and found to be composed of acetyl-sulfadiazine.		
Recovered—Right ureteral catheterization failed because of crystalline plaque covering right orifice. Left catheter left in situ and irrigated with warm distilled water. Bladder urine contained many crystals of acetyl-sulfadiazine.		

the wound. Also sulfadiazine was given by mouth gm. 1 q. 4 h. Her fluid intake varied between 1,500 and 2,000 c.c., but her output was difficult to determine because of incontinence. Three days after treatment was instituted, it was noted that her urine revealed a specific gravity of 1,010, albumin ++++, and an occasional red blood cell. Because of the possibility of sulfadiazine toxicity, the drug was discontinued. She had received a total of 22 gm. of the drug. Three days after cessation of the sulfadiazine, it was noted that she was markedly drowsy and semi-comatose. Non-protein nitrogen was 75, and blood level 12. Her urine was grossly bloody, and loaded with the crystals of acetyl-sulfadiazine. Because of her fracture, and her apparently terminal state, cystoscopy was deferred. A Foley retention catheter was inserted and the urinary output carefully measured. She was given intravenous fluids of 5 per cent glucose in distilled water alternating with Hartman's solution. She was also given sodium lactate by infusion, and sodium bicarbonate gm. 1 q. 4 h. by mouth to alkalinize her urine. In the first twenty-four hours, the output was 1000 c.c. and by the third day, the non-protein nitrogen was normal. She soon recovered from the ill effects of the sulfonamide drugs but died about two months later as a result of her fracture.

Case 9.—A fifty-nine-year-old man was admitted with a history of a sudden severe attack of pain in the left chest associated with cough and dyspnea. The physical findings were those of an enlarged heart with rapid fibrillation. The clinical diagnosis was that of bronchopneumonia of the left lower lobe in addition to a left ventricular failure in a rheumatic heart with auricular fibrillation. The temperature on admission was 102, pulse 150, urine negative. The non-protein nitrogen was 31, and a blood culture was positive for beta hemolytic streptococcus. The patient was immediately digitalized and started on sulfadiazine, being given 2 gm. at the start followed by gm. 1 q. 4 h. The fluid intake was about 2000 c.c. per day; the output was not accurately determined. Seven days after treatment was begun the temperature had returned to normal, and the clinical signs of pneumonia had disappeared. At this time, however, the patient complained of pain in the right costolumbar region, with marked dysuria, and frequency. His urine output was then about 1500 c.c. He had received a total of 38 gm. of the drug which was discontinued. Three days later he became drowsy. The urine output was 300 c.c. in twenty-four hours, the non-protein nitrogen was 60 and the blood level was 18.4. A flat radiograph showed a shadow suggestive of a calculus in the course of the left lower ureter. Cystoscopy was planned but because of a severe depression following morphine injection preliminary to the proposed cystoscopy, it was deferred. Fluids were forced by the intravenous route to 4000 c.c., the non-protein nitrogen dropped to normal, and the urine output returned to 3000 c.c. by the third day. The patient later passed the calculus which was shown on chemical and microscopic analyses to be that of acetyl-sulfadiazine.

Case 10.—A sixty-two-year-old white man was admitted with the chief complaint of pain in the right chest, accompanied by a severe chill and a productive cough. The physical findings were those of a right lower lobe pneumonia, and arteriosclerotic heart disease with fibrillation. The acid urine showed a definite trace of albumin and an occasional white blood cell. The non-protein nitrogen was 65. He was given 2 grams of sulfadiazine every four hours, followed by 1 gm. q. 4 h. His fluid intake varied between 1000 and 1500 c.c., but his output was not measured. After eight days of treatment, during which time he had received 36 gm. of the drug, it was noted that his output was about 100 c.c. The urine, smoky in appearance, had a specific gravity of 1.017, was decidedly acid, contained much albumin and was loaded with crystals of acetyl-sulfadiazine. The non-protein nitrogen was 140, the blood level 27.0. The patient complained of severe pain in the left loin and the cystoscopy was done. After introducing the instrument into the bladder, about 50 c.c. of urine passed through the cystoscopic sheath. The floor of the bladder and the trigone were covered with large masses of a crystalline substance which was washed out with difficulty. The left ureter was finally catheterized with a No. 6F catheter and a continuous drip of urine obtained. The right side of the ureteric ridge was covered with adherent crystalline plaques and consequently the orifice could not be catheterized. Because of his poor condition, no further manipulation was done; the left catheter was left *in situ* and irrigated q. 1 h. with warm distilled water. It was advised that the following solutions be given intravenously: 5 per cent glucose in distilled water, alternating with Hartman's solution to which sodium lactate was added. The patient gradually recovered entirely from the ill effects of the sulfadiazine.

DISCUSSION AND SUMMARY

In the analysis of these ten cases, it has not been our chief object to determine the relative frequency of severe toxic reactions following the use of sulfadiazine, but merely to report that they do occur. In this series, the drug was used in the treatment of five men and five women; the ages varied between fifty-two and ninety-three years; the clinical diagnosis in nine patients was that of bronchopneumonia or lobar pneumonia, and in one case, that of a fracture of the femur. In all the patients there was an associated arteriosclerotic heart disease, with varying degrees of congestive failure. The route of administration of the drug in all cases was oral, although in two patients intravenous administration was also employed. The patient designated as Case 3 received 32 gm. of sulfathiazole before sulfadiazine was given. The initial dose, as a

rule, was gm. 2 followed by gm. 1 q. 4 h. The time of onset of the major toxic symptoms varied considerably from three to twenty-one days, and in two instances, they appeared three and five days after the discontinuation of the drug because of minor toxic symptoms. The total amount of drug administered up to the point of the appearance of the symptoms varied from 12 gm. to 128 gm. This would seem to indicate that severe, and even fatal reactions might occur with as little as 12 gm. in as short a time as three days. A study of the fluid intake and urinary output in this series would perhaps indicate that in most cases sufficient attention was not given to this feature. It is of vital importance to force fluids to 2000 c.c. throughout the administration of the drug, and to carefully note the urinary output during this time so that it will not be allowed to fall appreciably. The urinary output dropped in all cases to 800 c.c. or less, and in four there was complete anuria; in all but two cases the output went below 500 c.c. Two of the patients showed an elevated non-protein nitrogen on admission, and in all the patients there was definite elevation of the non-protein nitrogen at the toxic point, the values varying from 40 to 180 mg. The recorded blood sulfadiazine levels varied from 12.2 to 32.2 mg.

It is interesting to note that the patient having a sulfadiazine blood level of 12.2 and a non-protein nitrogen of 64 died in anuria, while the patient with a blood level of 23.2 and a non-protein nitrogen of 180 (the highest in the series) recovered.

The therapy employed in those cases displaying anuria or suppression, gross hematuria, or increasing uremia, was to stop the drug at once. That concretions may exist without blocking the ureters has been demonstrated by many investigators. Under these circumstances, the treatment of sulfadiazine hematuria by means of forcing fluids alone seemed adequate, since we have evidence to believe that the concretions may be dissolved or washed out. If, however, complete anuria or suppression occurred, or if the possibility of a unilateral obstruction seemed evident, cystoscopy was done at once. Both ureters were catheterized, the catheters were left *in situ*, and irrigated every hour or two for at least two to three days. In most cases, where the obstruction had been overcome, adequate drainage established, and fluids forced, the blood level and non-protein nitrogen fell and the patient recovered. In

some instances, however, enough damage to the renal tubules and to the body as a whole may have occurred so that a fatal outcome was not surprising. We fully realize that in none of the patients who died can the cause of death be absolutely ascribed to sulfadiazine. The patients in Cases 1 and 2 were quite old when admitted, especially Case 1, and while autopsy showed yellowish sand in the right kidney pelvis, right ureter and bladder (presumably sulfadiazine crystals), this is still not the convincing evidence that is presented by the finding of sulfadiazine crystals in the tubules of both kidneys, which other observers have reported.

In Case 2 there is even less reason to place the blame on sulfadiazine because no crystals of sulfadiazine were found in the urine clinically or in any part of the urinary tract, postmortem. Still the fact remains that the patient's non-protein nitrogen rose rapidly after 12.5 gm. of sulfadiazine had been given and the patient soon became anuric. In the third patient who died there was anuria with bilateral residual urine in the kidneys, the ureteral specimens showing many crystals. Autopsy was not done in this case. In three of our other seven cases, there was bilateral ureteral obstruction due to calculi; in one there was unilateral obstruction, in two a severe gross hematuria, and in one no evidence of ureteral obstruction. This patient had a blood level of 23.2 and a non-protein nitrogen of 180 as probable evidence of severe damage in the kidneys themselves. Routine treatment was instituted in these seven patients and all recovered.

A consideration of these clinical facts and findings should impress one with the importance of the most careful observation of the patient who is taking sulfadiazine. Such a patient should receive at least 2000 c.c. of fluid daily and constant attention should be directed to the urinary output, the blood level of sulfadiazine and the non-protein nitrogen. The latter should be estimated at least every other day. Important danger signals of impending toxicity are the dropping of the fluid output below 1000 c.c., an elevation of the non-protein nitrogen and microscopic hematuria. When the sulfadiazine blood level becomes higher than 12 mg., the search for signs of toxicity should be redoubled. In patients having an acid urine an attempt at alkalinization should be made by giving sodium bicarbonate 1 gm. by mouth every four hours.

Certain observers feel that cystoscopic procedures as a thera-

peutic measure are rarely, if ever, necessary in the treatment of patients suffering from toxic renal symptoms of sulfadiazine. It is our belief, however, that in those patients where there is even the slightest question of obstruction due to calculi or crystals in the urinary tract (especially in the ureters), cystoscopy and probably ureteral catheterization should be performed without any hesitation.*

In conclusion, we wish to stress that no question is raised in this report of the therapeutic effectiveness of sulfadiazine, but we do express a serious doubt as to the prevalent feeling relative to the safety of the drug. We feel that in the course of time more of these reports will become available. We believe also that with careful management of the patient who receives this drug when indicated, its administration can be made fairly safe, especially if its potential pitfalls are kept in mind.

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*Plummer and Wheeler at the New York Hospital have observed sixty-three renal toxic reactions following the use of sulfadiazine or sodium sulfadiazine intravenously in 1,653 patients. In nineteen of the sixty-three cases, the only evidence of reaction was microscopic hematuria. In no case did the reaction progress to a real anuria. In every instance recovery occurred without any treatment other than discontinuing the sulfadiazine and maintaining an adequate fluid intake. In no patient was it found necessary to resort to cystoscopy and catheterization of the ureters.

DIVISION OF ABERRANT BLOOD VESSEL TO THE KIDNEY WITHOUT THE PRODUCTION OF AN INFARCT

REPORT OF A CASE

THOMAS SHUPE, M.D.
Cleveland, Ohio

In hydronephrosis due to aberrant blood vessels the surgeon is often confronted with the question of division of the blood vessel, especially if it be of good size, or whether he should undertake a division of the ureter and a re-implantation in a dependent portion of the kidney pelvis. Division of the vessel always has the future possibility of a renal infarct. Division and resuture of the ureter in the pelvis has the disadvantage of the suture line sloughing and scar tissue forming, making the condition such that nephrectomy is necessary. Numerous cases of aberrant renal vessels have been divided for hydronephrosis with good results and with no necessity for any further operation. Occasional cases, however, will show an infarct of such a size that nephrectomy will become necessary. That a large aberrant renal vessel the size of a slate pencil may be divided without causing a renal infarct is shown by the following case:

A young girl of sixteen complained of a mass in the upper left abdomen. This swelling had been noted casually for the past five or six years. The increased size of the mass was always accompanied by pain in the left abdomen and back. The mass was also tender and quite firm as it increased in size. These attacks had been infrequent until six months before admission, when the attacks became present every week and were so severe that the patient had to go to bed. After a few days rest in bed the mass would disappear and there was no more pain.

Cystoscopy and bilateral pyelograms showed a large hydronephrosis of the left side with obstruction at the ureteropelvic junction. At operation, an artery the size of a slate pencil was found coming from the aorta and entering the lower pole of the kidney. The aberrant vessel was in direct contact with the ureter close to the ureteropelvic junction and acted as a sling over which part of the extrarenal pelvis was dependent. At operation the aberrant vessel was divided and ligated and the scar tissue surrounding the ureteropelvic junction was freed by sharp dissection. The ureter then straightened out and the pelvis began to empty. A blanching of the posterior surface of the lower pole

of the kidney was noted. This blanching took in a third of the surface of the kidney. Neither the pelvis nor the kidney was incised.

The patient was free from pain and tumor for fourteen days, at which time the pain and swelling reappeared together with an elevation of temperature. Left nephrectomy was advised and performed. At the operation there was no sign of any difference in color or structure of the lower or upper pole. One part of the kidney seemed just

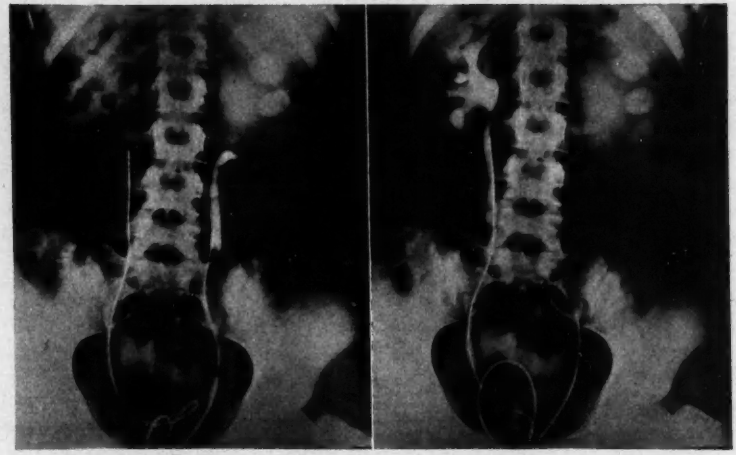

Fig. 1 (left). Hydronephrosis due to aberrant blood vessel.
Fig. 2 (right). Opaque media retained in hydronephrosis due to aberrant blood vessel.

as vascular as another. A large hydronephrosis was present and the ureter and kidney pelvis were bound down by a mass of adhesions. These were carefully dissected free from the pedicle and the kidney removed.

The patient had an uneventful convalescence following nephrectomy and left the hospital on the thirteenth day. Since then she has been perfectly well. The pathologic diagnosis was acute and chronic pyelonephritis with hydronephrosis. No infarct could be found in any part of the kidney. The uniform color and structure of the kidney were noted at the time of the nephrectomy, but no further thought was given to an infarct until the pathologic report was received.

PATHOLOGIC REPORT

Patient—M. G. Age 16. 5-12-41.

Diagnosis: Infected hydronephrosis following division of aberrant vessel.

Specimen: Left kidney.

Gross examination:

The specimen in formalin consists of a kidney measuring 13 x 5 x 4.5 cm.

and weighing 150 grams. The capsule for the most part has been previously removed, but in one small area where it is present it strips with slight difficulty. The external surface of the kidney is somewhat lobulated and contains many punctate hemorrhagic areas. There are a few small, shallow pitted depressions. The kidney sections with ease and shows the parenchymal substance

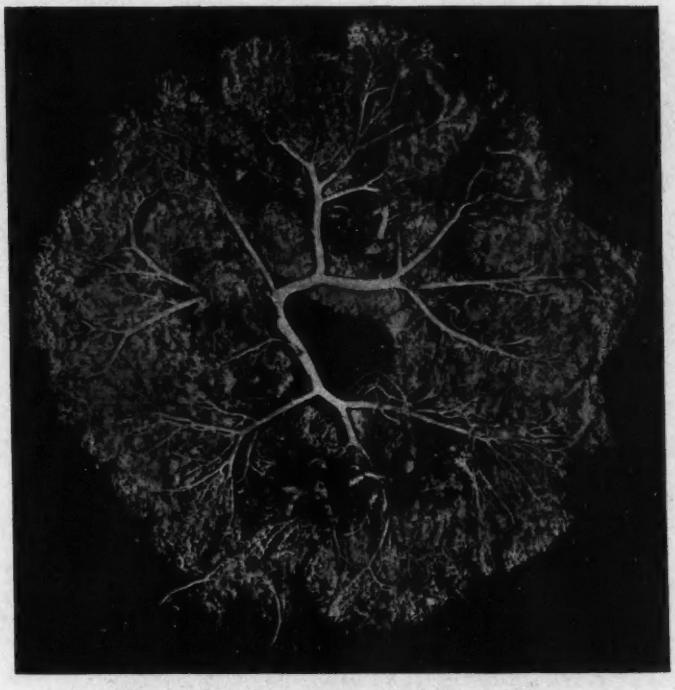

Fig. 3. Complete arterial tree of human kidney.

to be markedly thin. In certain areas it measures only 1.5 cm. in thickness. In some areas it is possible to differentiate between the cortex and medulla, the cortex measuring 0.6 cm. and the medulla 2 cm. The calyces and pelvis are markedly dilated, the walls are thicker than usual and very granular. Representative sections of the cortex, medulla, and pelvis are taken.

Impression: Kidney the seat of pyelonephritis and extensive hydronephrosis.

A. MACON LEIGH, M.D.

Histologic examination:

Sections taken from various portions of the kidney show essentially the same histologic appearance and will be described together. The normal architecture

can be recognized but it is considerably distorted by exudation of large numbers of cells and proliferation of young fibrous connective tissue, especially in the cortical zone. The cells in the cortex are principally polymorphonuclear leukocytes although some eosinophiles and lymphocytes are also present. In the medulla the lymphocytes are relatively more prominent and in sections taken through the renal pelves the cellular exudate is almost entirely lymphocytic.

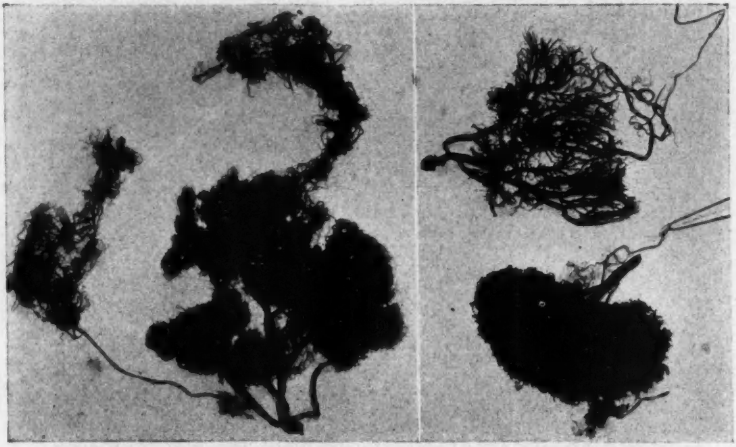

Fig. 4 (left). Collateral circulation occurring in human kidney.
Fig. 5. (right). Collateral circulation occurring in human and dog kidney.

In many areas the tubules contain leukocytes and the tubular epithelium shows various degrees of swelling and granulation.

The glomeruli are well formed and contain no leukocytes. There are no glomerular abscesses. Most of them contain blood. The arterioles and arteries present an essentially normal microscopic appearance.

Diagnosis: Acute and chronic pyelonephritis with hydronephrosis.

WILLIAM B. WARMAN, M.D.

Patient—M. G. Age 16. 5-12-41.
Diagnosis: Infected hydronephrosis following division of aberrant vessel.
Specimen: Left kidney.
Additional note:

Both the gross material and the microscopic sections have been reviewed in this case and careful examination shows no infarct in any part of the kidney.

WILLIAM B. WARMAN, M.D.

That the kidney does have at times, and not infrequently, collateral circulation to various areas has been mentioned by Dr. Fran-

cis Bayless, and has been demonstrated by Helen Lieb, both of the Institute of Pathology of Western Reserve University.

These demonstrations have been made on kidneys by injecting the renal artery with neoprene, a liquid rubber in an alkaline medium, and a semi-solid rubber in an acid medium. After the arterial system is injected, the kidney tissue is dissolved by means of dilute hydrochloric acid. It is the opinion of Dr. Bayless that an artery arising from the aorta or the spermatic is more likely to supply the capsule than a vessel arising from the renal artery. In other words, it is safer to divide an aberrant vessel to the kidney arising from any other source than the renal artery.

BILATERAL ADRENAL CORTICAL TUMORS

REPORT OF A CASE SIMULATING RENAL NEOPLASM

CHARLES P. HOWZE, M.D.

Washington, D. C.

In recent years, many advances have been made in our knowledge of the functions of the normal adrenal gland. These facts have in turn stimulated considerable clinical and experimental investigation of its various complex pathologic states, particularly in regard to hyperplasias and tumors. A very comprehensive analysis of these facts has been made in an excellent paper by Cahill, in which he discussed the embryology, histology, and physiology of the normal and pathologic gland, and presented a sound clinical classification of cortical tumors. The literature is becoming voluminous with reports of both cortical and medullary types, correctly diagnosed, and of patients cured by surgical removal of the tumor. Many such cases have been presented to this association by its members. The opposite has been true in regard to bilateral adrenal tumors. It is for this reason that I am reporting a recent case and also giving a brief review of the literature.

R. H. M., a white man, aged fifty-one, was referred to me on March 26, 1940, because of a right lumbar mass and a deformity of the right renal pelvis noted in an excretory urogram. There had been no symptoms referable to the kidney at any time. He had suffered no lumbar or abdominal pain.

A résumé of his history since December 8, 1936, by his physician was as follows: Mr. M. first consulted this office on December 8, 1936. At that time he was forty-eight years of age. His chief complaints were fatigue, loss of weight, and prostatitis. He stated that before his vacation in September, he had been very much exhausted. He found it difficult to concentrate and was irritable and nervous. Five years before he had had a prostatitis which had been improved by treatment but had recently recurred. Following a tonsillectomy in 1934, he had lost 41 pounds in weight, having declined from 206 to 145 pounds. There was a loss of libido of five years' duration, with slight improvement following prostatic massage. A complete diagnostic study was done and the following diagnoses made: Chronic prostatitis, fatigue syndrome, and alveolar abscesses. Treatment was instituted for these conditions, fatigue became less marked, and he gained 7 pounds in weight in the next three months.

In January, 1939, he was again examined at the insistence of his

wife, who felt he was below par. At this time, he had two dead teeth which were under observation. His weight had remained stationary around 170 pounds. The blood pressure was systolic 134, diastolic 84. He had had a burning sensation in the throat for the past year. The basal metabolic rate was minus 16. One-half grain of thyroid three times a day was prescribed. In April, 1939, four abscessed teeth were reported, and he was advised to have all of his remaining teeth re-

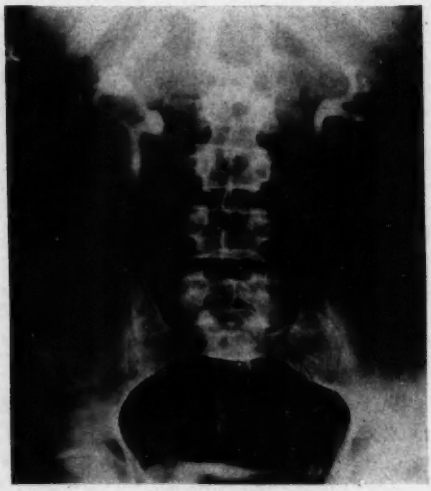

Fig. 1. Excretory urogram revealing deformity of the right renal pelvis.

moved, and replacements made. Tonic medication with vitamin B and thyroid were prescribed. All teeth were removed and he had gotten replacements when seen in June, 1939.

The patient returned on December 1, 1939. Since his previous visit he had lost 10 pounds, and his wife and associates felt that he was looking badly and failing in health. At this time blood studies revealed: Hemoglobin 90 per cent; red blood cells 4,600,000; leukocytes 8,000; polymorphonuclears 72 per cent; lymphocytes 28 per cent. In February, 1940, an x-ray study of the intestinal tract was done because of loss of appetite and gagging which he attributed to his plates. No organic disease was found. On February 5, 1940, the basal metabolic rate was again minus 16. Urinalysis was negative both chemically and microscopically. The blood non-protein nitrogen was 39 mgm. Hemoglobin was 80 per cent and red blood cells 3,800,000. This represented a slight reduction in his blood count of one year previously.

Fatigue became more marked, and on physical examination in March, 1940, an enlarged and freely movable right kidney was found. An excretory urogram revealed a deformity of the right renal pelvis characteristic of cortical renal neoplasm. The left pelvis appeared normal. At this time the patient was referred to me.

On physical examination a smooth, freely movable, rounded mass the size of a large grapefruit was noted in the right lumbar region. Following a study of the excretory urogram, a diagnosis of right renal tumor was made, and x-ray therapy followed by right nephrectomy was advised (Fig. 1). X-ray therapy was begun on March 29, 1940, and 200 r were given daily for seven days. The patient tolerated the therapy poorly, and nausea and vomiting became so pronounced that he was hospitalized on April 5. There was marked soreness of the mouth, throat, and gums. Blood studies at this time revealed an aplastic anemia and a severe leukopenia. Hemoglobin was 54 per cent, red blood cells 2,620,000, and leukocytes were only 950. The differential count was as follows: Polymorphonuclears 46 per cent, lymphocytes 52 per cent, and eosinophiles 2 per cent. This seemed definitely to rule out agranulocytosis. He was treated intensively with daily blood transfusions, parenteral glucose, and Hartmann's solution, and with thiamine chloride intramuscularly, until his death on April 14, 1940. There was some improvement in the blood picture, in that the red blood cells were elevated to 3,600,000 and the leukocytes to 1,400, with 84 per cent polymorphonuclears. The urine was normal except for a trace of albumin and numerous coarsely granular casts. Temperature fluctuated between normal and 104 degrees. There was a terminal bloody diarrhea for two days preceding death.

A summary of the clinical picture reveals a progressive asthenia with loss of weight, soreness of the mouth, throat, and gums resulting in gagging, loss of appetite, nausea and vomiting, a progressive anemia with a terminal marked leukopenia, and a low basal metabolic rate. A painless mass was discovered in the right loin twenty-four days previous to death. No discoloration of the skin or mucous membranes was apparent.

Autopsy report (Dr. Janvier Lindsay, Friday, April 14, 1940): The only gross findings of interest were the tumors of both adrenal glands and a small nodular metastatic tumor in the myocardium. Both adrenal glands were greatly enlarged, the normal pattern being almost completely replaced by lobulated masses of yellowish tissue, with pink streaking, radiating from the central areas toward the outer edge. On the right side this tissue was seen to continue into the hilum of the kidney and to replace in an expansive development practically the entire kidney, leaving only a narrow, incomplete shell of essentially normal renal pattern. The left kidney was not involved in the neoplastic process. The tumor of the adrenal gland in each case appeared, for the most part, to be rather sharply marked off from the kidney, or the kidney and invading tumor below, respectively. Right adrenal tumor

measured approximately 10 cm. vertically, 18 cm. transversely, and 6 cm. anteroposteriorly. The kidney on this side with the included tumor mass measured practically the same as the adrenal. On the left side the diameters of the tumor mass were transversely 10 cm., vertically 7.5 cm., and anteroposteriorly 4 cm. The kidney on the left measured 7 cm. by 10 cm. by 4 cm. (Fig. 2). Paraffin sections from various parts of the tumor and kidney showed a generally uniform structure

Fig. 2. Gross: right and left kidney showing adrenal tumors, with metastasis or extension to right kidney.

of epithelial cells, evidently of glandular type. The cells were large, usually clear, with round or oval nuclei occupying about 20 to 25 per cent of the cell body. Throughout the sections there was a definitely tubular or papillary glandular arrangement. In all sections there were occasional cords or groups of cells in which the cytoplasm was deeper staining and more granular than in the majority. In the sections taken from the mass replacing the adrenal there were a number of cells in cords or groups, with the typical morphology of the cortical cells of the adrenal. There appeared to be a clear transition from these cells to those of the tumor proper. It was therefore believed, from the gross and histologic examination, that the lesion was a cortical adrenal carcinoma (Figs. 3 and 4).

The metastatic nodule in the heart muscle was similar in the histologic study to that of the original adrenal tumor (Fig. 5).

A brief résumé of the microscopic examination of the other tissues removed at autopsy was reported as follows: Pancreas: Sections showed marked infiltration by fat between the lobes of the gland. The gland structure was normal. Heart: The fibers were normal in size and staining qualities. There was very little sclerosis of the small vessels. In one section there was a small nodular metastasis from the

adrenal tumor. This was very papillary in structure. Lungs: Many areas showed dilated and empty alveoli with thin noncongested walls. The appearance here was entirely normal. Other sections showed moderate atelectasis with congestion (grade 3). Bone marrow: Section showed normal cellular constituents reduced in amount. There were fairly numerous normoblasts present, indicating active erythropoiesis.

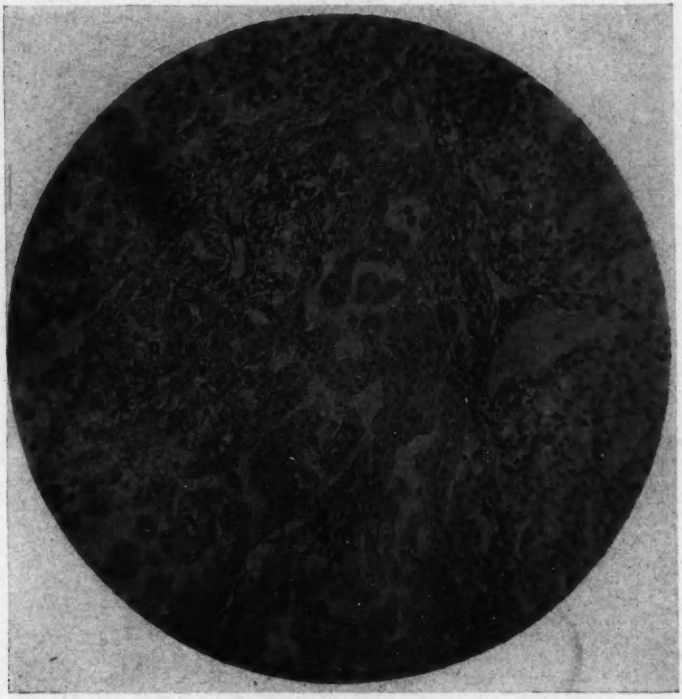

Fig. 3. Right kidney. Microscopic section of tumor identical in region of adrenal, kidney and heart muscle.

Kidney: Section showed the glomeruli to be normal in size and slightly congested. The tubular epithelium was swollen and desquamating (grade 2). There was no vascular disease present. Spleen: Sections showed severe passive congestion with gross extravasation of blood into the splenic substance. There was severe sclerosis of the vessels. Liver: Sections showed swelling of the liver cells, which were filled with coarsely granular cytoplasm. There was diffuse vacuolization (grade 4).

I have found in a review of the literature on adrenal tumors from 1850 to the present time sixty-six cases of bilateral tumors of various types. There are two specimens in the Army Medical Museum not yet reported, which make a total of sixty-nine cases. Forty-five of this group appear to be true cortical tumors arising

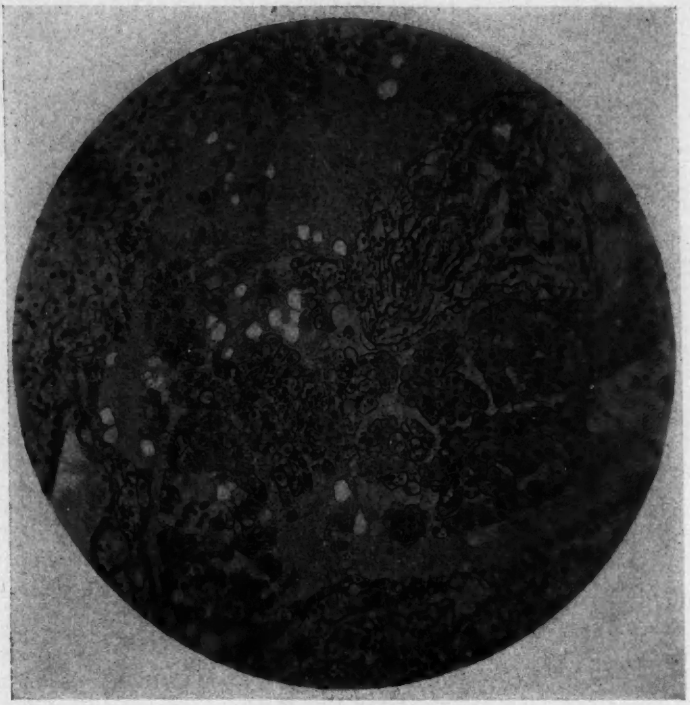

Fig. 4. Left kidney. Microscopic section of tumor identical in region of adrenal, kidney and heart muscle.

from the adrenal cortex cells and are cytologically adenomas and carcinomas. Six bilateral paragangliomas are reported. The remainder are classified as sarcomas of various types, melanomas, cavernous angioma, and one retroperitoneal cyst of undetermined character. In all cases the diagnosis was made at autopsy except in the case of retroperitoneal cyst, the origin of which was doubtful.

It is possible that some of the cases reported as sarcomas might be true adrenal cell tumors.

The youngest of these cases was found in a male child, four days old, and the tumors were described as adenomatous hyper-

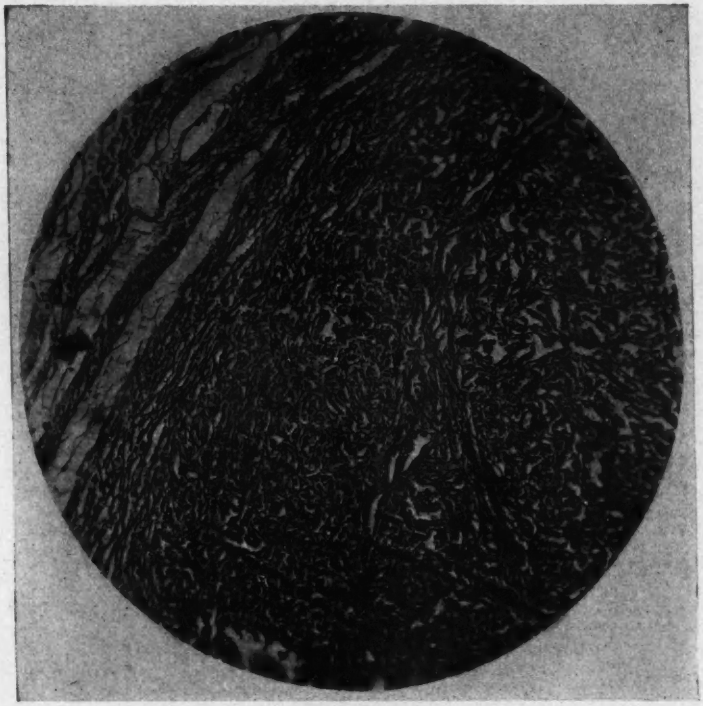

Fig. 5. Microscopic section (lower power) of tumor in heart muscle.

trophy. The oldest true cortical tumors were found in a man aged sixty-eight. The majority of cases occurred in the fourth and fifth decades of life.

There were thirty-six men, twenty-five women, and the sex was not mentioned in five. One case is reported in a pseudo-hermaphrodite aged fifty, which appears to be the only hormonal type tumor in the entire group.

The diagnosis was not made in a single instance during life.

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
Besnier	1850	M	48	Paresthesia of lower extremities; lumbar pain radiating to extremities	—	Section revealed whitish pulp interspersed with reddish spots; no trace of original tissue; four to five metastases in kidney	Found at autopsy
Mettenheimer	1856	M	47	Peculiar brownish-gray discoloration of skin; incessant pain in lumbar region	—	Evidence of microscopic study inconclusive but indicative of either carcinoma or spindle celled sarcoma	Found at autopsy
Döderlein	1860	M	45	Tympanites; edema of legs; dullness over lower portions of lungs; dyspnea; purulent expectoration; ascites; remittent, fulminant, lancinating abdominal pains	—	Medulla of both suprarenals replaced by soft, black, marrowlike masses surrounded by intact yellow cortex; metastases to celiac glands, left kidney, liver, peritoneum, omentum, lungs, bronchial glands, left cerebral hemisphere	Found at autopsy
Duclos	1863	F	36	Bronzing of skin; cessation of menses; impeded gait from lumbar pain; mild sudation; systolic murmur at apex	—	Scirrhus tumors	Found at autopsy
Greenhow	1866	M	56	Pain down course of the right sciatic nerve and other symptoms attributed to malignant disease of vertebrae; partial paraplegia; appearance of hard, supposedly cancerous nodules on surface of chest	—	Large mass of malignant matter surrounded and replaced lumbar vertebrae and pancreas; similar formations in substance of heart, cellular tissue of chest, under pleura, in liver, both psoas muscles; and in cellular tissue surrounding pelves of kidneys, suprarenal capsules similarly infil-	Autopsy

				cerous nodules on surface of chest		liver, both psoas muscles; and in cellular tissue surrounding pelves of kidneys; suprarenal capsules similarly infiltrated	
Meyer and Schweninger	1875	F	71	—	—	Probably lymphosarcoma	Report of autopsy
Haussmann	1876	M	62	—	—	Hypernephroid tumor; metastases in practically all organs, especially stomach and intestines	Report of autopsy
Klebs	1876	M	11	—	—	Primary suprarenal tumor	Report of autopsy
Birch-Hirschfeld	1877	M	54	—	Cancer of liver	No microscopic examination	Found at autopsy
Rosenstein	1881	M	40	Anorexia, general debility, lumbar, later gastric pain radiating downward to left and gradually increasing in severity	—	Small celled sarcoma (primary)	Found at autopsy
Schuchardt	1883	M	38	—	—	Primary carcinoma; metastases to abdominal aorta and vena cava, gall bladder, small intestine, spleen, thrombosis of thoracic duct	Found at autopsy
Turner	1885	M	25	Initial symptoms of bronchitis relieved temporarily by medical treatment; subsequent signs of consolidation of left lung, emaciation, debility; no pyrexia	—	Greatly enlarged suprarenal bodies situated at extremities of horseshoe kidney with its convexity downward; suprarenals infiltrated with soft medullary growth, associated with mediastinal tumor of similar character invading left lung from its root; microscopic examination of sections of bronchial gland infiltrated by growth showed round cell sarcoma	Autopsy

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR (Continued)

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
Fraenkel	1886	F	18	Palpitation, anxiety; intermittent headache; increasing debility	Albuminuric retinitis	Angiosarcoma (right); sarcoma (left)	Observed at autopsy
Hadden	1886	M	64	No evidence of Addison's disease	—	Pyloric orifice of stomach sharply narrowed by firm mass; right suprarenal converted into large firm pale growth; left suprarenal somewhat smaller and infiltrated with firm growth; microscopic examination showed carcinoma, in which numerous hemorrhages were seen	Autopsy
de Ruyter	1890	—	—	—	—	Lymphosarcoma teleangiectodes haemorrhagicum (right); congenital lymphosarcoma (left)	Found at autopsy
Marchand	1891	*	50	—	—	Both glands transformed into an enormous tumor; entire medullary substance consisted of almost uniformly proliferated suprarenal tissue	Observed at autopsy
Leva	1891	F	46	—	Addison's disease	Hard, nodular tumor size child's head, yellowish gray on section and enveloped by tougher white substance (right); smaller similar tumor (left)	Report of autopsy
Orth	1893	F	58	—	—	Melanosarcoma of left suprarenal, with metastases to right suprarenal, pia mater, brain,	Report of autopsy

Orth	1893	F	58	—	—	Melanosarcoma of left suprarenal, with metastases to right suprarenal, pia mater, brain, lung, liver, lymph nodes	Report of autopsy
Jores	1894	M	30	—	—	Microscopically both tumors consisted of short, minute fusiform cells with moderately large spindle shaped nuclei arranged in rows	Report of autopsy
Stoukovenkoff	1895	F	50	Pain over liver, hemoptysis; edema of legs; albuminuria; dyspnea; cyanosis	—	Carcinoma, metastases to liver and lungs	Autopsy
Weinberg	1895	M	56	Chronic laryngeal lesion	—	Primary pavement-celled epithelioma of larynx; adenoma of suprarenal capsules associated with so-called fatty suprarenality	Autopsy
Chauffard	1896	M	37	Syndrome of neurofibromatosis; color of skin earthy and dusky; numerous pigmented areas distributed chiefly over skin of trunk and lumbar region	—	Histological study of various sections revealed bilateral symmetrical capsular degeneration of cortical origin suggestive of adenoma rather than epithelioma	Autopsy
Pawlik	1896	F	50	Anorexia, vomiting; pollakiuria; right facial paralysis; right hemiplegia; involuntary passage urine and feces	—	Melanotic carcinoma; metastases to right kidney, brain, lungs, pleurae, epicardium, endocardium, peritoneum, liver, uterus	Autopsy
Castaigne	1897	M	—	—	—	Sections from 3 zones: peripheral, cancerous; median, purulent; central, degenerated; microscopically, peripheral zone and glands suggested adenocarcinoma; 2 other zones without characteristic structure	Autopsy

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR (Continued)

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
Chaillons	1897	M	27	Anorexia, occasional delirium, evening temperature without apparent cause 14 days before death	—	Microscopically, peripheral zone exhibited cell-groups arranged in regular parallel rows with interjacent trabeculae of connective tissue; internally, cells were more numerous, scattered, and connective tissue thickened	Autopsy
Weinberg and Turquet	1897	F	36	Gastric dilatation; diarrhea; lumbar pain; vomiting; severe headache	—	Carcinoma, with metastases to both lungs, cerebellum and appendix	Autopsy
Brooks	1898	F	49	Irregular temperature; emaciation; pain down left leg from involvement of lumbar nerves	—	Secondary growths in liver, lungs, left kidney, by continuity, right suprarenal; left suprarenal seat of carcinoma of anomalous aspect	Autopsy
Mandlebaum and Libman	1898	M	61	Pain in chest, cough, bloody expectoration; no tubercle bacilli in sputum	Malignant tumor of lung	Both lungs showed dense whitish masses extending along bronchi and infiltrating pulmonary parenchyma; chronic interstitial nephritis; mass size of orange above and firmly attached to each kidney, right soft, left firm and nodular; large glandular mass near head of pancreas; microscopic examination revealed lymphosarcoma; right adrenal apparently primary seat of involvement	Autopsy
Sty'br	1899	—	—	—	—	Primary medullary	Autopsy
Sty'br	1899	—	—	—	—	Carcinoma	Autopsy

						of involvement	
Sty'br	1899	—	—	—	—	Primary medullary	Autopsy
Sty'br	1899	—	—	—	—	Carcinoma	Autopsy
Baucke	1899	—	—	—	—	Soft, nodulated tumors size of goose egg, revealing on section white as well as finely striated portions traversed by numerous vessels; metastases to retroperitoneal and bronchial lymphatic glands, left main bronchus and hilus of lung	Autopsy
Petroff	1899	F	38	Skin markedly pigmented, exhibiting a bronze tint especially around navel, over breasts, and nape of neck	Addison's disease	Cavernous angioma of both suprarenals and of liver	Autopsy
Carriere and Delearde	1900	M	54	Edema of legs; cachexia; diarrhea; pleural effusion; ascites	—	So-called atypical epithelioma, with metastases to liver and lungs	Autopsy
Pal	1901	F	53	Anorexia, gastric pains, vomiting, emaciation	—	Sarcoma of right suprarenal with metastases to right kidney and left suprarenal; glioma of temporal lobe of right hemisphere and encephalomalacia of meditullium profundum	Autopsy
Schittenhelm	1901	M	55	Pains in left leg and renal region; five days before death expectoration, diarrhea, rigor, signs of inspissation over lungs; occasional vomiting; Cheyne-Stokes	—	Microscopically, infiltration of fairly large round or angular pavement cells with short oval, fairly large nucleus, between them very scanty connective tissue abundantly provided with vessels, suggesting an alveolar structure; metastases to liver, left pleura, pericardium, and renal cortex	Autopsy

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR (Continued)

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
Warthin	1901	M	4 days	Total suppression of urine for twenty-four hours; frequently repeated convulsive movements; severe opisthotonos	—	Adenomatous hyperplasia in both adrenals and probably also in left adrenals of Marchand, associated with retrograde alterations in right adrenal of Marchand	Autopsy
Kulyosh	1902	F	68	—	—	Papillary adenoma (struma maligna); pigment in both suprarenal tumors; metastases in peritoneum, liver, kidneys, lungs, and heart	Autopsy
Reimann	1903	M	3 mos.	Rapid emaciation, debility	Gastro-enteritis	Congenital primary suprarenal tumors	Autopsy
Holst	1904	M	49	Anorexia; emaciation; marked abdominal protrusion (right)	Carcinoma of pylorus	Malignant, metastasizing tumors arising apparently from suprarenal cortex; in metastases as well as tumors proper microscopic picture suggested carcinoma	Autopsy
Holst	1904	M	37	Pulmonary tuberculosis	—	Mixed celled sarcomas (presumably metastases of a sarcoma which had originated elsewhere)	Autopsy
Ivanisoff	1904	—	—	Exudative pleuritis	—	Small round-celled sarcoma, primary in suprarenals, secondary in lung	Autopsy
Breton and Looten	1905	F	57	Generalized severe abdominal pain especially along lower margin of liver; emaciation;	—	Markedly enlarged kidneys surmounted by an enormous capsule enveloped in sarcomatous	Autopsy

croscopic examination revealed bilateral

Looten				dominal pain especially along lower margin of liver; emaciation;		enormous capsule enveloped in sarcomatous	
						croscopic examination revealed bilateral small celled sarcoma of suprarenals with secondary involvement of kidneys as well as mesenteric ganglia	
Froin and Rivet	1906	F	56	Hemiplegia (left), contracture, Babinski sign	—	Histological examination revealed nodular (adenomatous) formations of cortical layer of suprarenals	Autopsy
Froin and Rivet	1906	M	57	Hemiplegia (left), no ictus	—	Both suprarenals presented definite adenomatous masses	Autopsy
De Besche	1907	F	68	Severe gastric pain unrelated to ingestion of food, vomiting; unproductive cough	—	Tumors of undetermined character	Autopsy
Winkler	1909	M	50	—	—	Tumors characterized histologically by perivascular arrangement of epithelium, grouped in double rows around external walls of a vessel	Autopsy
de Vecchi	1910	F	33	—	—	Lymphangiectasis, with secondary cystic formation	Autopsy
Lascagna	1910	M	61	Cough	—	Paraganglioma (?) general structure showed giant cells, mosaic appearance, abundance of capillaries; positive chromaffin reaction; no metastases	Autopsy
Gilbert and Whitman	1911	F	36	Progressive languor, debility, emaciation; pain and swelling of ankles; slight unproductive cough; nausea, abdominal tenderness	Generalized tuberculosis; articular manifestations of latter;	Bilateral adrenal sarcoma with metastases in lung simulating miliary tuberculosis	Autopsy

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR (Continued)

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
					involvement of mesenteric and retroperitoneal glands		
Herde	1912	F	45	Hypertension	—	Bilateral paraganglioma; frequent giant cells; abundant glycogen in left tumor; cardiac hypertrophy	Autopsy
Prym	1913	F	46	—	—	Adenoma or hypernephroma	Autopsy
Antonelli	1922	M	62	Polycythemia rubra; incomplete Addisonian syndrome	—	Carcinoma of upper lobe of right lung, with diffuse metastases in suprarenals	Autopsy
Biebl and Wichels	1925	M	36	Hypertonia, arterio- and arteriolosclerosis, and glycosuria of presumed adrenalinogenous origin	—	Paraganglioma (chromaffinoma) of both suprarenals	Autopsy
Manganotti	1925	F	41	Headache, nausea, frequent vomiting of matter with extremely bitter taste and greenish color, persistent pain in right scapular and lumbar region; no icteric tint; scant urine of dark reddish color; painful micturition	—	Bilateral sarcoma of suprarenals with cardiac metastasis	Autopsy
Smith	1927	M	64	Abdominal pain, vomiting, loss of weight, pain in umbilical region after ingestion of food	Carcinoma of stomach	Bilateral adrenal melanoma; no metastases	Autopsy
King	1931	M	30	Loss of weight; pains	—	Malignant paraganglio-	Autopsy
				cutaneous nodules on chest and abdomen		liver, lungs, bones, brain; positive chromaffin reaction	

King	1931	M	30	Loss of weight; pains	—	Malignant paraganglio-	Autopsy
				cutaneous nodules on chest and abdomen		liver, lungs, bones, brain; positive chromaffin reaction	
Pepino	1931	F	63	—	—	Hypernephroma, or suprarenal adenoma (atypical or malignant hypernephroma)	Autopsy
Laederich, Mamou and Beauchesne	1932	F	55	Typical Raynaud syndrome accompanied by rheumatoid pains without fever, progressive scleroderma associated with deep pigmentation of skin, marked emaciation, cachexia	—	Bilateral cortical adenoma	Autopsy
Lazarus and Eisenberg	1932	F	62	Progressive thyroid enlargement; nodule on left lower gum following extraction of tooth; loss of weight and strength; mass in right renal region	—	Malignant pheochromocytoma; metastases to liver, lungs, bones, intestines, glands, and gum	Autopsy
Levinson	1932	F	40	Periods of depression associated with vertigo and coincident with menstruation; sensation of pressure upon chest with precordial pain; cephalalgia; lancinating pains and tics of left side of face; nausea; pain and vomiting after meals (vomit frequently bloody); difficult micturition and frequent tenesmus; lumbar pains	Retroperitoneal cysts (radiologic)	Retroperitoneal cysts of undetermined character	Removed at operation
Puech, Rimbaud and Dufoix	1932	M	45	Fatigue, abdominal pains, generalized brownish discoloration of skin, emaciation, moderate edema of lower limbs, abdominal distention, liver enlarged and	—	Bilateral benign corticosuprarenaloma	Autopsy

CHRONOLOGICAL REVIEW OF REPORTED CASES OF ADRENAL TUMOR (Concluded)

Author	Date	Sex	Age	Symptomatology	Diagnosis	Pathology	Remarks
				painful, marked tachycardia, hypotension			
Mueller-Stueler	1933	F	77	Ileus, cardiac weakness, constipation	—	Bilateral cavernous hemangioma	Autopsy
Luse	1935	M	54	Pain in left side of abdomen and down left thigh, frequency of urination, loss of weight	Malignancy left lung	Extensive hypernephroma involving both adrenals with metastases in mediastinum and left lung	Autopsy
Minovici and Bonciu	1936	M	37	Symptoms of food poisoning	—	Histologically tumors consisted of polymorphous epithelial cells, also giant cells, many with very large nuclei, all surrounded by network of fibrils of connective tissue rich in sinusoidal capillaries; cytoplasm homogeneous, finely granular, eosino- or basophile	Autopsy
Goormaghtigh	1940	M	53	—	—	Alveolar carcinoma composed of large polyhedral cells with fine granular acidophil protoplasm fairly rich in collagen; histologically adrenal tumor of cortical origin	Autopsy
Wahl	1942	M	38	Cough, pain in abdomen and chest	Hypernephroma (tumor) right adrenal gland	Malignant paraganglioma with metastases to lungs, kidneys, pancreas, diaphragm, small intestine, mesenteric and supraclavicular lymph nodes	Autopsy
Howze	1942	M	53	Marked asthenia; nausea; loss of weight; mass in right lumbar region; vomiting	—	Bilateral suprarenal adenocarcinoma	Autopsy

Addison's disease was diagnosed in two cases and hypernephroma in one.

There seems to be no classical picture of symptoms or signs by which it is possible to diagnose bilateral adrenal tumors. Rowntree states that any pathologic lesion which gradually destroys the suprarenal bodies may produce the characteristic symptoms of Addison's disease, at least in part. He also says that the adrenal medulla is not essential to life and that the cortex is concerned with (1) the growth of tissues, (2) the organs of reproduction, (3) the intake of food and its assimilation, and (4) the transformation of energy. To further complicate the picture, however, all other glands of internal secretion seem to be concerned in some way or other with nutrition, growth, and reproduction.

In view of the rather confused picture, one is at a loss as to when to be suspicious of bilateral cortical tumors. It would seem reasonable to consider the diagnosis in a patient of middle age, with a history of progressive weakness, progressive anemia, rapid loss of weight, nausea and irregular vomiting and diarrhea, and a lowered basal metabolic rate, when all findings fail to discover other pathologic conditions. If improvement in symptoms is noted after injections of a potent cortical adrenal extract, might it not be an indication for using air insufflation as a method of positive diagnosis?

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PSEUDOHERMAPHRODITISM DUE TO HYPERACTIVITY OF THE ADRENAL CORTEX*

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and (by invitation)

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This presentation is a preliminary report on two cases of pseudohermaphroditism in young women associated with hyperactivity of the adrenal cortex; the so-called adrenogenital syndrome. While these cases are not rarities, we feel they will be of interest.

The subject of hermaphroditism has attracted the curiosity and interest of mankind from the most ancient times and instances are mentioned by writers, medical and otherwise, of every period. We will not attempt to give a complete historical outline as this has been thoroughly covered in other works.[14, 20] We will review, briefly, the outstanding points relating to the type of case under discussion.

The association of abnormalities of the adrenal cortex with cases of hermaphroditism dates from the eighteenth century.[20] The first cases noted were those with tumors, which were found at postmortem examination. The occurrence of bilateral adrenal hypertrophy associated with hermaphroditism was first reported in 1816 and several similar cases were reported at intervals during the nineteenth century. An etiologic relationship was suspected by some of these men, but it was not until 1891 that Marchand asserted his belief that there was a definite connection between the hermaphroditic state and the presence of excessive adrenal tissue in the form of adrenal enlargement and of adrenal rests.

In 1908 von Neugebauer, in his encyclopedic treatise on hermaphroditism,[14] enumerated thirteen cases in which there was an associated hypertrophy of the adrenal glands. In 1910 Apert[1] published a series and made the first attempt at classification according to age of onset—a grouping which, with some modifications, is in use today. The subject lagged somewhat, but there was a revival in interest in the 1930's, along with the renewed study of the other endocrine glands. In the last few years, there has been much

work and investigation of the many functions of the adrenal cortex and the isolation and chemical identification of the various adrenal cortical hormones. Collections of cases and reviews of the literature have been published by Young,[20] Cahill,[5] Goldzieher,[8] Broster, et al.,[2] Walters and Kepler,[18] and others. Young's is the most comprehensive work. There have been many recent publications relating to the strictly chemical and endocrine aspects of the question. Excellent recent reviews are those of Wintersteiner[19] and Cahill.[5] Reilly, Lisser and Hinman,[15] in 1939, collected all the cases in young girls up to that time.

The adrenogenital syndrome has been defined as a condition in which functional and, usually, anatomic changes in the adrenal cortex are associated with changes in the sexual characteristics. There are a number of clinical forms. It occurs much more frequently in women than in men. The genital changes in women consist of suppression of normal female secondary sex characteristics and accentuation to a marked degree of male secondary sex characteristics.

In other words, in the female there is a clinical condition of virilism. The body contours are more angular and more muscular. The shoulders are relatively wider than the hips. Hair growth is increased and masculine in distribution with male pubic escutcheon, increased hair on body and limbs and sometimes a growth of the beard. There may be acne of face and body. The larynx is prominent and the voice is deep. Breast development is absent, the mons veneris is flat. The clitoris is enlarged and may resemble a hypospadic penis. The vagina may open into the urethra. The internal genitalia are usually normal but undeveloped. In the most marked cases there may be an hypertrophy of the peri-urethral glands, forming a "prostate." In these cases erection and ejaculation may occur, the ejaculate consisting of the secretion of the "prostate." Psychic reversion of varying degree towards the masculine is sometimes present and can be complete. Associated with these genital changes there is usually precocious somatic development in the child, and in some cases obesity.

The earlier in life the onset of the disturbance occurs, the more marked will be the deviation from normal. It is in the case where the disease begins in prenatal life, that the clinical characteristics are so marked as to constitute a pseudohermaphroditism. Onset

after birth, but in the prepubertal period, causes less alteration in body structure, but usually suppresses appearance of the normal female pubertal development. Onset in adult life causes the smallest degree of bodily change, and symptoms in these cases may be limited to hirsutism, amenorrhea, obesity and slight voice changes.

In the male the adrenogenital syndrome occurs very infrequently. In boys, it leads to precocious puberty and sometimes obesity. In the even more rare adult form, it can lead to feminization.

There are a few other clinical conditions which are closely associated with adrenal cortical hyperactivity, such as Cushing's syndrome or basophil adenoma of the pituitary and the Achard-Thiers syndrome or diabetes of bearded women. In these conditions there are disturbances of the nongenital functions of the adrenal cortex, with or without genital changes.

The anatomy of the adrenal glands is of considerable interest because it gives some clue to the close association between the adrenals and the gonads. The medulla arises from the sympathetic nervous tissue. It is entirely separate from the cortex in origin and function and is unrelated to the present subject.

The cortex arises from the mesodermal lining cells of the celomic cavity at a point just medial and immediately adjacent to the site of origin of the gonad. The cortex is made up of epithelioid cells arranged in masses and cords in three layers, the outer the zona glomerulosa, next the fasciculata and the reticularis. In addition to these zones, there appears another in the fetal gland, the so-called androgenic or x-zone. This appears regularly in two species, the man and the mouse. This zone, described by Grollman,[9] is quite large early in fetal life. He says that it is due to this extensive x-zone that the adrenals are so large in fetal life, being at one stage as large as the kidneys. At birth, the adrenals are about one-third the size of the kidney and diminish relatively in size from this point on; the decrease, according to Grollman, being due chiefly to degeneration of the x-zone. Besides the adrenal cortex proper, there are, in many individuals, accessory nodules or rests of adrenal cortical tissue along the course of the gonadal vessels and also frequently about the internal genitalia, most commonly between the leaves of the broad ligament.

The anatomic changes found in the adrenal glands in cases of adrenogenital syndrome are not constant and vary all the way

from almost no gross abnormalities to large malignant tumors. Some deviation from normal is demonstrable, however, in nearly all cases. In one group of patients a simple or nodular hyperplasia occurs, in which case the lesion is generally bilateral. There may be definite discrete adenomas which again may be bilateral. Finally, there may be true carcinomas capable of metastasizing widely. Any of these lesions can arise also from rests of adrenal tissue lying outside the borders of the normal gland. All of the above mentioned pathologic changes have been found to occur without any endocrine or clinical symptoms.

Broster and Vines and their colleagues,[2] not being able to find any consistent anatomic or microscopic abnormality in the glands they removed, tried various staining techniques. By the use of the ponceau-fuchsin stain, they believed they were able to show a pathognomonic staining reaction in the cortical cells which, in adrenogenital cases, stained differently from the cells in normal glands. Goldzieher[8] has demonstrated hyperplasia of the juxtamedullary zone in some of his cases.

In addition to the lesions of the adrenal itself, in some cases brought to autopsy changes have been noted in the pituitary gland. In females, atrophy of the ovaries is almost universally found with hypoplasia of the female internal genitalia.

At the present time, one is not able to enumerate with certainty and completeness all the functions of the adrenal cortex.[11] We know that the cortex is necessary for life. About twenty different compounds have been isolated from adrenal cortical extracts and there is no one of them which completely serves all the functions of the adrenal cortical gland. The usually mentioned functions of the adrenal cortex are regulatory effects on (1) carbohydrate metabolism, (2) muscle response to stimulation, (3) distribution of electrolytes, (4) renal function (blood flow and tubular re-absorption), (5) body growth, (6) resistance to stress and low temperature and (7) reciprocal effect on the activity of the anterior pituitary.

The exact place, if any, of the normal adrenal cortex in the physiology of the genital system is not yet determined. Some men feel that the adrenal cortex is necessary to completely normal function of the gonads, especially the testis, but the extent of this functional dependency is indefinite. It is known that injection of

certain steroid hormones, including androgens, causes atrophy of the adrenal cortex, while injection of estrogens causes adrenal cortical hypertrophy.

The most probable hypothesis at the present time is somewhat as follows:[2, 19] it is known that the adrenal cortex is capable of elaborating and secreting steroid hormones of both androgenic and estrogenic nature. Such substances have been definitely isolated and their chemical formulas determined. The secretion of such genital hormones in the normal adult is probably small in amount and overshadowed by the output of the normal gonad. Although not functioning as a sex gland in the adult, there is a strong probability that the adrenal cortex does so in fetal life. A number of facts such as, the large size of the fetal adrenal, the x-zone and staining characteristics of the fetal gland, tend to support this theory. At one time during fetal development in both males and females, the adrenals go through a very definite androgenic phase. According to this hypothesis, then, the adult adrenal cortex is potentially a source of androgenic hormone and the adrenogenital syndrome is due either to a continuation or a resumption of the genital function which is normally confined entirely to the prenatal period.

One cannot say definitely at the present time whether this output of androgenic substance is the function of certain cells or of certain zones of the cortex. This idea, previously advocated by Grollman,[9] Goldzieher[8] and others has some evidence to support it. There are others again who believe that the elaboration of this androgenic substance is a function of any or all of the cells of the cortex and that abnormal androgenic output is due merely to an altered metabolism of these cells rather than re-activation of an entirely different type cell.

The etiology of malignant tumors of the adrenal cortex is as obscure as that of tumors elsewhere. As yet no one has been able to answer the question as to the basic or fundamental disturbance in the cases of bilateral hyperplasia. It is frequently a congenital disturbance and may be familial. It is impossible even to say definitely, at the present time, whether the primary disturbance is in the adrenal itself, or whether it is in the pituitary or in the gonad.

As mentioned previously, pituitary changes have been found in

some cases of adrenogenital syndrome, but it is not a consistent finding. Cases of Cushing's syndrome may have adrenal cortex hypertrophy and clinical features of the adrenogenital syndrome with additional symptoms indicative of disturbance of the non-genital functions of the adrenal cortex.

We will not consider fully the endocrine aspects of this subject although much work is being done at the present time. We might briefly say that the urinary androgen output is almost invariably increased, along with the output of pregnandiol and similar substances. Output of estrogen is usually not increased in hyperplasias but may be quite high in some tumors. Wintersteiner's review[19] has this complicated subject well summarized with an excellent bibliography.

Because of lack of knowledge of the exact etiology of these disturbances, treatment, of course, is symptomatic and empiric. We know that the adrenal cortex is hyperactive and usually hyperplastic and the most effective treatment, so far, has been directed towards the removal of adrenal cortical tissue. In the case of tumors, removal of the tumor is the obvious course. Where there is no definite tumor unilateral adrenalectomy has been done by some,[28] and bilateral partial adrenalectomy by others.[20] The difficulty is to determine how much can be removed safely. If too much is removed symptoms of dangerous adrenal cortex deficiency may occur. While this may be corrected by substitution therapy, chronic deficiency is certainly a condition to be avoided if at all possible. Before removal of the entire adrenal, the presence and size of the opposite gland should always be determined. X-ray treatment has been used in a few cases with some remission of symptoms reported.

There is another form of treatment which might be useful in this type of case. It is well established that adrenal cortical atrophy can be induced by administration of various steroid hormones in comparatively small doses. We do not know whether such a method has been tried in this type of case or whether it would be efficacious. It would be indicated only in cases of bilateral hyperplasia and not in the presence of tumors. We are considering its trial before removal of more tissue in these cases if regression of virilism is not satisfactory.

CASE REPORTS

Case 1.—The patient, a fourteen-year-old white girl, was referred to the Research and Educational Hospital, October 3, 1941, for exact determination of sex before commitment to a state children's home. She had been abandoned by her parents.

The patient was our only informant and her history was as follows:

She had been raised as a girl and had always played with girls. She knew, however, that she had always had an enlarged clitoris. At the age of nine, she noticed that this enlarged quite rapidly. Two years ago, at the age of twelve, dark hair appeared on the face and elsewhere on the body; at the time of admission, she shaved once a week. Menses also began at twelve and have appeared at regular thirty-day intervals since. The patient was unable to say whether her voice changed at any certain period. She denied having had any sexual experiences with either boys or girls.

Her parents were living and well. Her father had been committed to a mental institution for firing a gun at a neighbor's house. She had two young brothers living and well and a sister, aged two, who, according to the patient, had a large clitoris and a deformity similar to the patient's. The patient also reported that two maternal aunts had somewhat similar conditions. We have not been able to verify this.

Previous medical history included only whooping cough at nine years of age, followed by pneumonia.

She had never had any formal schooling.

The patient presented the appearance of a rather muscular child of fourteen with body characteristics of the male type. Weight was 106½ pounds; height, 60 inches. The skin was rather dark, the hair brown. There was some acne of the face and shoulders. Muscular development was fairly marked, as of an active boy rather than of a girl. Over the face there was a moderate growth of rather heavy, coarse, black hair. The gums were spongy and the oral hygiene was poor. The chest was muscular and over the sternum in the axillæ and around the nipples there was a growth of black hair. There was absolutely no breast development.

The physical findings relating to heart and lungs were normal. The blood pressure was 116/80. The abdomen was flat and muscular and there were no masses or other abnormalities in the abdomen and none could be felt in the kidney region. The lower extremities were covered with a fairly heavy growth of black hair and were muscular.

Genitalia: There was marked growth of suprapubic hair with male type of escutcheon extending up to the umbilicus. There was a rather large phallus about 2 centimeters in diameter and about 4 centimeters long, hypospadic type with ventral curvature. At the base of this phallus was what at first seemed to be a urethra; however, on closer examination, a vaginal orifice was seen and, on spreading, the urethral

orifice could be seen immediately inside. It was possible to do a vaginal examination with one finger and the small, apparently normal uterus was palpable. No masses were found in the pelvis.

Cystoscopic examination revealed a normal bladder and urethra.

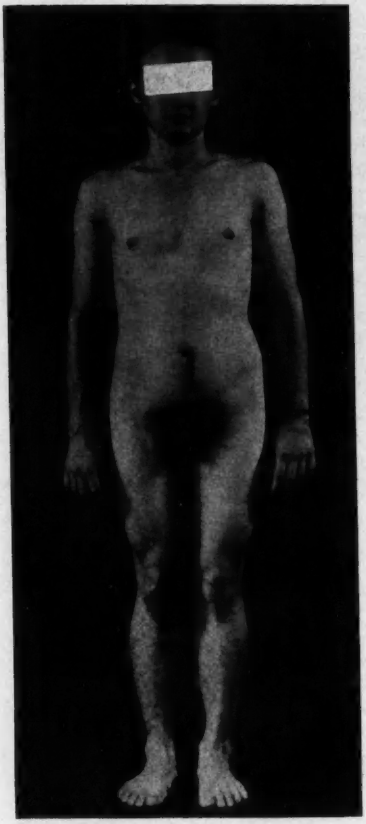

Fig. 1. Case 1. Front view, pre-operative.

Fig. 2. Case 1. Genitalia, pre-operative.

Laboratory analyses revealed the following:

Urine: Normal specific gravity, no sugar or albumin, negative microscopically.

Blood: Red blood cells 4.2 mm. hemoglobin 100 per cent, white blood cells 6.1m, Wassermann and Kahn negative. Blood glucose 65

mg., non-protein nitrogen 39 mg., uric acid 4.3 mg., chlorides 457 mg., cholesterol 170 mg., serum albumin 4.2 mg., serum globulin 1.9 mg., CO_2 46 c.c./100 c.c. Glucose tolerance—fasting, 80 mg.; one-half hour, 109 mg.; one hour, 98 mg.; two hours, 79 mg.; three hours, 100 mg.

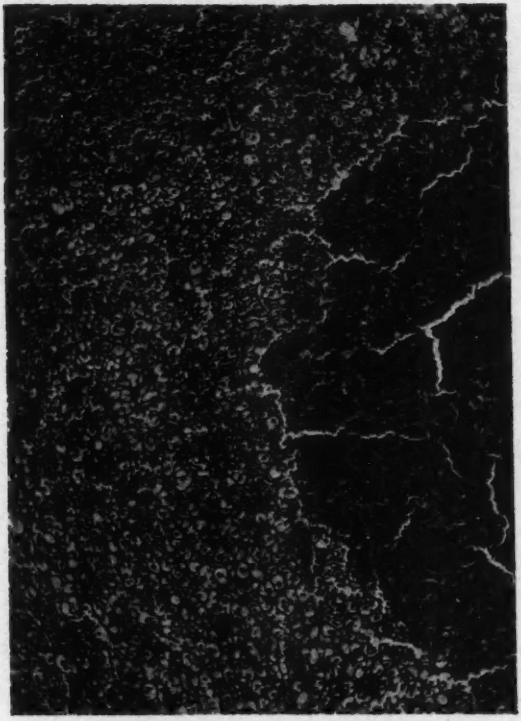

Fig. 3. Case 1. Low power section, right adrenal, simple hyperplasia.

Basal metabolism rate: –6 per cent.

Radiographs of the skull, sella, wrists and knees showed closed epiphyses. Nothing abnormal was found in the plain film of the urinary tract and intravenous urogram with diodrast showed no abnormality or displacement of the kidneys. Films made after injection of 240 c.c. of air into the perirenal space showed the adrenals quite well with the following measurements: 28x65 mm. on the right and 30x75 mm. on the left.

Approximately one month after admission (November 7) an exploratory laparotomy was done (Dr. Falls) through a subumbilical midline incision. A uterus was present which was normal in size for the patient's age. Both ovaries were present although they appeared undeveloped. Small sections were taken from each ovary for biopsy. No other abnormalities were seen. No gross enlargements could be found in the region of the adrenal glands and no accessory adrenal tissue was noted.

Sections of the biopsies from the ovaries showed immature underdeveloped ovaries with primordial follicles present in both sides.

Three weeks later (December 1) under general anesthesia, with the patient flat on her face, both adrenals were exposed through incisions parallel with the spinal column. The left adrenal was brought down and measured about 2x2x1.5 centimeters and the right about 4x3x3.5 centimeters.

Since the right seemed considerably larger than the left, about three-fourths of the right gland was resected. A section, about 1 centimeter in diameter, was removed from the left gland chiefly for biopsy purposes and the incisions were closed with Penrose drains on either side.

She received 10 c.c. of eschatin during the operation (6 c.c. intravenously, 4 c.c. intramuscularly). Postoperatively, she was given saline solution intravenously and 5 c.c. of eschatin later that day. She received two doses, of 5 c.c. each, of eschatin on the first postoperative day and one of 3 c.c. on the second postoperative day.

Blood pressure was maintained well during the operation. At no time did the systolic pressure fall below 110 or the diastolic below 70. In the evening of the first postoperative day, the pulse became rapid and thready and the blood pressure dropped to 90/60. One of the 5 c.c. doses of eschatin was given intravenously at that time and intravenous fluids started. She responded quite promptly and there was no further similar attack.

The pathologic diagnosis was diffuse hyperplasia of the right adrenal cortex.

While the patient was still in the hospital, the clitoris was amputated and the perineum opened more widely to establish a more normal female condition of the genitalia. There was some drainage from the right side incision over a period of several weeks, but the patient's general condition improved steadily.

The seventeenth postoperative day there was an elevation of temperature to almost 101 degrees accompanied by some tenderness on the right side. However, this receded within a few days and there was no further trouble. When she left the hospital, her beard was a little less marked and there was possibly a slight rise in the pitch of her voice.

An examination, five months postoperatively (May, 1942), revealed general good health. The voice was slightly higher but still coarse. She shaved only once every ten days to two weeks. The body con-

tours were much less angular and more feminine and there was slight breast development. The patient was quite pleased with these changes.

Case 2.—A white female child, aged four and one-half years, was first admitted to the Research and Educational Hospital March 28, 1941. The child had had a normal delivery and weighed 8 pounds at birth. The attending physician noticed immediately after birth

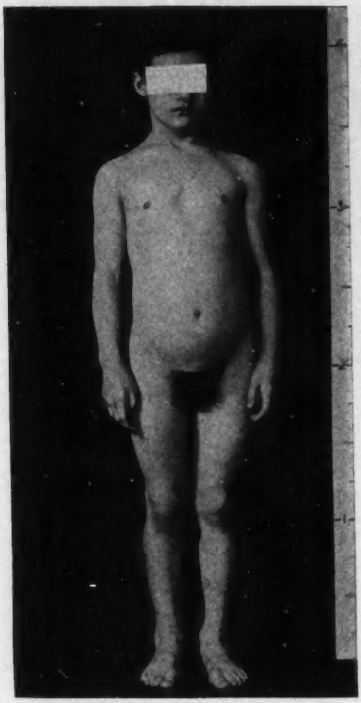

Fig. 4. Case 2. Front view, pre-operative. Age—four and one-half years.

Fig. 5. Case 2. Genitalia pre-operative.

that the genitalia were abnormal but said that the child was predominantly female. The child developed normally otherwise until the age of two, when the parents noticed a growth of hair over the pubic area which progressed rather markedly so that at the time of admission, there was hair in the axillæ. After the age of two, the child grew quite rapidly and was very strong for her age. She was above

average mentally; could say several words plainly at the age of one and could write her name and count at four. Her voice became quite coarse and low in pitch at the age of three.

She had chicken pox at eight months, and measles at three years. There was no familial history of any similar condition. There were no other children. There were no pathologic symptoms of note.

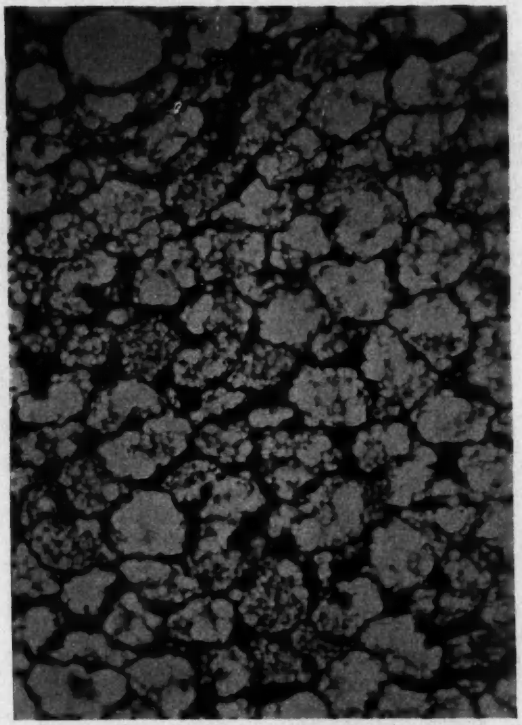

Fig. 6. Case 2. High power section, right adrenal adenoma.

Physical examination revealed a very well developed white child, aged four and one-half, weight 30.5 kilograms, blood pressure 115/78. The voice was quite deep. General body contour was symmetrical and the child was quite muscular. The skin was clear; no abnormal pigmentation. The eyes and eyebrows were normal. There were a few black axillary hairs. There was no breast development. The abdomen was normal. No masses could be palpated in the kidney regions. There was thick, black, coarse pubic hair.

Examination of the genitalia revealed a large phallus, 2 centimeters in diameter and 4 centimeters long. There was considerable ventral curvature and, on the ventral surface, there was a groove lined by shiny mucosa. There was a perineal urethral meatus and no division of this canal could be seen by spreading the meatus with the fingers.

Manual rectal examination failed to reveal definite palpable organs.

A 20F cystoscope passed easily under general anesthesia (seconal), revealing a normal bladder. About 2 centimeters from the bladder the vaginal opening was seen and when the cystoscope was introduced, a normal appearing cervix was seen, through which the ureteral catheter could be introduced for 5 centimeters.

In the laboratory analyses, the urine's specific gravity was 1.005, no sugar or albumin, microscopically negative.

Blood: Red blood cells 5.3 mm., hemoglobin 15 gm, white blood cells 7.0 m. Wassermann and Kahn negative, glucose 67 mg, non-protein nitrogen 33 mg, chlorides 450 mg, CO_2 58 c.c./100 c.c., cholesterol 148 mg, serum albumin 5.8 mg, serum globulin 2.6 mg. Glucose tolerance—fasting, 67 mg; one-half hour, 103 mg; one hour, 68 mg; two hours, 97 mg.

Radiographs of the skull showed normal sella, no evidence of pituitary enlargement. Films of the wrists showed precocious bone development which would be consistent with the age of almost twelve years. Plain radiographs of the abdomen revealed normal findings. After injection of dye intravenously, the kidneys were visualized and showed bifid kidney on the left side but no other abnormality. Films made after injection of a catheter in the uterine cavity outlined the interior of the uterus and vagina.

Endocrine findings: The gonadotropic hormone was less than 66 mouse units per liter (normal); estrogenic substance—0 (normal); 17 ketosteroids—37 mg for twenty-four hours (two times adult male); pregnanediol—0 to 20 mg for forty-eight hours (normal—no output).

Her psychologic examination rated an I.Q. of 112. The examining psychiatrist felt that this was probably too low to express accurately the mental development.

An exploratory laparotomy (Dr. Falls) was done through a low midline incision passing to above the umbilicus; the pelvic organs were exposed and examined. A small but structurally normal uterus, tubes and ovaries were found. Biopsies were taken from the ovaries. The abdominal cavity was examined for aberrant adrenal gland tissue but none was found. Attempt was made to palpate the adrenal glands. The right was felt to be hazelnut size, the left smaller. The right seemed to be of normal consistency with no tumor masses.

The tissues taken from the ovaries were essentially the same from both sides and showed immature primordial follicles and ova. There was an unusual amount of fibrous tissue surrounding the follicles

and it was judged that the ovaries had undergone some degenerative or atrophic changes.

After this exploration, the child left the hospital to return later, but because of extraneous circumstances did not do so until March, 1942.

Injection of air in the perirenal space on the left side showed the left adrenal to be approximately 20x30 mm. in outline. The right was not outlined. Assured of the presence of this left adrenal, the right was exposed through a posterior incision with the patient flat on her face. The adrenal was not grossly abnormal. However, three-fourths of the gland was resected and the incision closed with drainage.

She received 3 c.c. of eschatin intramuscularly before the operation. The blood pressure remained good throughout the operation. At the finish of the operation it was 140/90. Taken at intervals during that day and the next two days, it never fell below 110/60 and no further eschatin was given. Saline and a blood transfusion were given postoperatively as well as sodium chloride by mouth.

Examination of sections led to a diagnosis of (1) cortical adenoma of adrenal; (2) diffuse and focal pseudonodular hyperplasia of disordered adrenal cortex.

Case 3.—A white female child, aged ten years, was brought to the Research and Educational Hospital, November 17, 1939, because the mother noted an abnormality of the genitalia. At birth the child was thought to be a girl. At sixteen months, the mother noticed that the genitalia were not strictly feminine and that there was an abnormal increase in the size of the clitoris. At three years, there was a growth of hair in the axillæ and in the pubic region. At this time also, the mother thought that the child's growth was abnormally rapid. At the age of five, the child's voice began to change and became lower in pitch. The rapid body growth continued. At this time, the mother said the child began to play boys' games rather than with dolls, et cetera. When five and one-half, the child was placed in school as a girl and has continued as such.

The body growth increased steadily until the age of nine years when growth stopped completely. Although she had been attending school with girls, her recreation had been with boys (baseball, football, et cetera). The hair growth increased and was quite profuse. There were no other symptoms except that glasses had been prescribed at the age of seven.

The patient was a second child, full term, labor three hours, forceps delivery, weight 8 pounds. Development in the first year was apparently normal. Her sister was normal and there was no history of similar condition in any relatives or any other disease in the immediate family.

Physical examination revealed a well developed, muscular appearing child, 55¾ inches tall, weight 99¼ pounds, appearing to be thir-

teen or fourteen years of age. The voice was deep and the general muscular development marked, the shoulders wide. The temperature, pulse and respiration were normal and the blood pressure 120/80.

The hair was normal in texture. The pupils were normal and re-

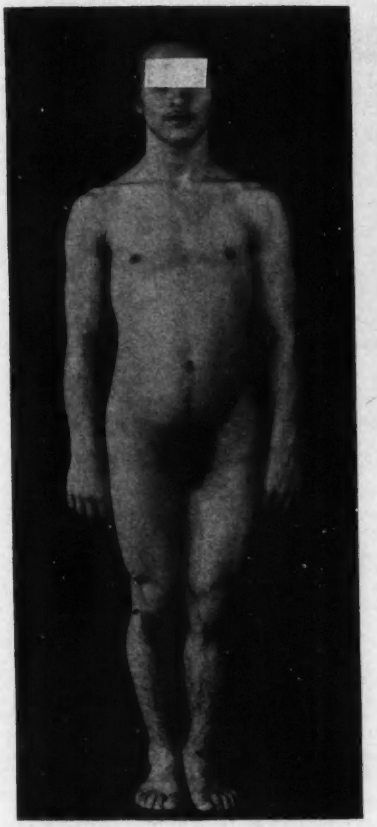

Fig. 7. Case 3. Front view.

Fig. 8. Case 3. Genitalia.

acted normally. There was a moderate facial growth of hair. The chest was well developed and there was a heavy growth of axillary hair. There were no abnormal chest findings. The breasts were completely undeveloped. The abdomen was muscular and there were no masses. There was a heavy growth of suprapubic hair with male

escutcheon. Extremities were well developed and muscular with rather profuse growth of hair.

There was a large phallus, 2¼ centimeters in diameter and 5 centimeters long, well developed glans with ventral curvature. There was a dimple at the apex of the glans and along the ventral surface a shallow, mucosa-lined groove with several glandular pockets visible. At the base of the phallus was the urethral meatus.

Rectally, nothing resembling the prostate was found and bimanual palpation did not elicit any definite information. The labia were pigmented but no masses were palpable either in the labia or in the groin. There was no history of bleeding from the urethra at any time. No history of erections could be elicited.

Fundus examination was normal. Visual fields were normal. Myopia was present in both eyes.

Cystoscopic examination under local anesthesia revealed a normal bladder. The vagina connected with the urethra about 2 to 3 centimeters from the bladder. By passing a panendoscope into the vagina, a small cervix was seen with a visible opening into which a catheter could be passed for 4 or 5 centimeters.

Examination by the psychiatry department elicited the information that her tendencies were almost entirely masculine. She was in the sixth grade, doing well in her subjects and wished to study medicine. She did boy's work around the house, such as tending the lawn, and disliked domestic work. She had no close girl associates, preferred athletics and other sports with boys. She enjoyed reading, especially scientific books. She showed no evidence of sexual interest in either boys or girls, but said she did not like girls. Her sister, fifteen years old, has been interested in dress designing. The patient very definitely expressed her desire to be a boy. Her I.Q. was 118.

The clinical laboratory reports were as follows:

Urine: specific gravity 1.010, sugar and albumin negative, no cells, few phosphate crystals microscopically.

Blood: Red blood sells, 6.1 mm; hemoglobin, 14.5 gm; white blood cells, 7.3 m; Wassermann and Kahn, negative; non-protein nitrogen, 36 mg; creatinin, 1.5 mg; uric acid, 2.9 mg; chlorides, 479 mg; cholesterol, 185 mg; calcium, 7.9 mg; phosphorus, 4.5 mg. Glucose tolerance—fasting, 90 mg; one-half hour, 161 mg; one hour, 182 mg; one and one-half hours, 150 mg; two hours, 130 mg; three hours, 78 mg. No urine sugar at that time.

Basal metabolism rate: 7 graded on weight; 20 graded on height.

Endocrine findings: 17 ketosteroids—30 mg for twenty-four hours (two times normal male) in 1939; 69 mgs for twenty-four hours (four times normal male) in 1941. The gonadotropic examination

in 1939—66 mouse units per liter (normal), estrogenic substance—0, pregnandiol—0.34-19.7 mg for twenty-four hours (definitely above normal).

Radiographs of the skull showed sella normal. Wrists and knees showed precocious ossification with epiphyses closed.

Intravenous urogram showed kidneys normal in position and outline. Injection of opaque dye showed the vagina definitely outlined.

Diagnosis of probable adrenal cortical hyperplasia or possibly tumor was made. The patient's parents did not give permission for either perirenal air injection or exploratory laparotomy. It was impossible to impress them with the necessity of a complete investigation for a final decision as to the sex which the child should follow in later life.

Our arguments were without any appreciable effect. The parents, of foreign birth and not overly intelligent, submitted to the child's decision, and at her insistence, moved to another neighborhood, clothed her in boy's attire, gave her a boy's name and transferred her to a different school. This is her status at the present time, approximately two and one-half years after we first saw her.

The cases presented here are of a congenital type with onset probably in the fetal period. Two have had subtotal unilateral adrenalectomy. If necessary, more tissue can be removed from the other side in either case, or endocrine therapy can be given a trial. It is too early to give end results but they seem to be favorable in the patient who was operated on six months ago.

While there is no emergency in these cases in young girls with benign conditions, we do feel that treatment should not be postponed indefinitely as advocated by some.[10] These children usually have advanced osseous development and this sometimes leads to premature closure of the epiphyses. If this occurs too early the patient may be dwarfed to some extent, as illustrated in one of our cases. We feel that it is best to get these cases entirely straightened out in as early a stage of life as is possible. The intersexual state is usually accompanied by various psychic and social difficulties which may be lessened or obviated by early attention. Changes or adjustments in the sexual sphere are relatively much more easily made in the case of the young child as compared to the difficulties associated with such a change in the adolescent or adult. Therefore, in our opinion, the earlier remedial surgery or treatment is carried out, the better it will be for the patient, family and all concerned.

SUMMARY

The subject of female pseudohermaphroditism, due to the adrenogenital syndrome in female children, is briefly reviewed.

Two cases proven at operation are presented. In a third case the diagnosis has been made clinically, but permission for verification has been refused and the child is now being raised as a boy.

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DISCUSSION

DR. HUGH H. YOUNG (Baltimore, Md.): Doctor Shupe's paper on the division of aberrant blood vessels to the kidney is very interesting. His demonstration that they can be divided without the production of infarct is important. I now usually employ an anterior abdominal incision in these cases.* The incision begins at the outer side of the rectus muscle, about 1 inch above the pubes, and is directed obliquely upward and outward to the cartilage of the tenth rib. The incision, in fact, passes over that so as to make a longer skin incision and allow wider retraction. The fascias and muscles are divided and then the peritoneum stripped back until the ureter is exposed at a point several inches below the kidney. Following the ureter upward and continuing the separation of the peritoneum, the uretero-pelvic juncture is exposed as it lies in its natural position and then the pelvis above it. This affords an excellent opportunity to study the pathology in situ before it has been disturbed by freeing the kidney and drawing it far out, as must occur where the usual lateral oblique kidney incision is employed.

In the case of which the motion picture was shown, a thick vascular cord was found passing across the uretero-pelvic juncture to the lower pole of the kidney. Associated with it were pronounced adhesions which were divided. Above the vascular cord the ureter was markedly kinked and entered the pelvis beneath the vascular cord. Although the adhesions were freed, the considerably dilated pelvis did not empty itself until the vascular cord had been elevated, triply clamped and divided. Immediately after this the ureter straightened out and peristalsis began.

The motion picture shown demonstrated beautifully successive peristaltic waves which started in the pelvis as it gradually emptied and passed down the uretero-pelvic junction and along the ureter. These were so active that the ureter actually was seen to move and twist, almost like an earthworm. Investigation showed that no stricture of the ureter was present, only a thinning of the wall at the point where it was compressed by the vascular cord. After division of the cord, a small area of the lower pole of the kidney

*A motion picture in color by Mr. William P. Didusch, depicting the technique employed in one of these cases (BUI 31705) was shown. The case was one of hydronephrosis due to obstruction produced by a vascular cord just below the uretero-pelvic juncture.

turned bluish-black in color. The rest of the kidney appeared normal.

In cases such as this one, it is not necessary to isolate the lateral, upper and posterior surfaces of the kidney at all. At the ureteropelvic juncture any pathologic conditions which may be discovered can be attacked often at once without disturbing the kidney in its bed or isolating the vessels of the pedicle. In these cases where the obstruction is due to aberrant vessels, one almost always finds that they pass in front of the ureter. This is another argument for the anterior incision which is also applicable in cases of kinks, strictures, and particularly appropriate where the Y-V plastic is carried out. If it is desirable to perform nephropexy, no difficulty is experienced in isolating the kidney and carrying out an appropriate technique through this same incision. Where it is desirable to expose the ureter well down towards its lower end, the anterior incision has much to recommend it, inasmuch as one can easily follow the ureter down to its juncture with the bladder and do a complete nephro-ureterectomy through one incision. The anterior incision is also of great advantage where in wounds and other types of traumatism it is desirable to explore the peritoneal cavity and perhaps operate upon some other viscera, as is often the case in war surgery.†

In this technique I find it desirable to provide drainage through a stab wound over the crest of the ileum. This gives a direct retroperitoneal external dependent drainage which is always desirable for a few days. If one wishes to drain the lower end of the ureter, another Penrose drain or tube may be brought out through the lower angle of the oblique abdominal incision.

[During the demonstration of the motion picture, the following question was asked.]

DR. CHARLES C. HIGGINS (Cleveland, Ohio): Do you believe it is necessary to ligate the aberrant vessel? The primary causative factor is strangulation of the ureter, isn't it? If you sever the adhesions and straighten out the ureter, do you think that the aberrant vessel will maintain a hydronephrosis?

DR. YOUNG: In the patients upon whom I have operated, the vascular cord apparently obstructed the ureter and caused the an-

†Young, Hugh H: Wounds of urogenital tract in modern warfare. Jour. Urol., 47:59-108, (Feb.) 1942.

gulation or sigmoid curve and the obstruction at the uretero-pelvic juncture.‡ Until I have tied the vascular cord, the obstructive kink in the ureter has never been eliminated. When the artery supplies only a small part of the lower half of the kidney, no great injury seems to follow its ligation.

DR. HIGGINS: I think in this case the primary cause of the hydronephrosis is angulation of the ureter and probably congenital adhesions. There is an aberrant vessel there. If you hadn't had the angulation, you would not have had the hydronephrosis.

DR. YOUNG: How do you prove which comes first? I rather think that the aberrant vessel pressing upon the ureter led to the kinking and obstruction.

DR. HIGGINS: In many autopsies I found quite a similar condition without the presence of hydronephrosis. The ureter is straight.

DR. VINCENT J. O'CONOR (Chicago, Ill.): In discussion of Dr. Jeck's paper, I would like to present a case which I think is extremely interesting in regard to a late anuria following sulfathiazole therapy.

H. P., aged thirty-nine years, white, traffic manager, entered the hospital complaining of vomiting, epigastric distress, hiccough, scanty urine and subconjunctival hemorrhages for the past four days.

The patient felt "quite" well up to four weeks ago. He was a chronic alcoholic and consumed a pint of whiskey every day. After an alcoholic debauch four weeks ago, he developed a "cold" and cervical lymphadenopathy and was given 45 grains of sulfathiazole daily for four days. He had apparently recovered until four days ago. Persistent vomiting, sleeplessness, urine suppression and abdominal fullness continued.

The throat and lungs were clear, the heart normal, with a blood pressure of 115/170, the abdomen soft; liver, kidneys and spleen not palpated; no masses, tenderness or rigidity of abdomen. The red blood cell count was 3,860,000; hemoglobin, 78 per cent; white blood cells, 11,100; polys, 92; lymphocytes, 7; eosinophiles, 1; urine output the first day 20 c.c. in twenty-four hours: analysis, 100 mg. albumin, no sugar, 10-12 blood, 10-15 pus, urates and moderate number of epithe-

‡Young, Hugh H.: Obstructions to the ureter produced by aberrant blood vessels. A plastic repair without ligation of vessels or transplantation of ureters. Surg., Gynec. and Obst., 54:26-38, (Jan.) 1932.

lium cells in centr. sediment, occasional cast, no sulfathiazole crystals found. Blood chemistry: NPN 115 mg., creatinine, 3.5; serum chloride 550; total cholesterol 100; esters 58 per cent.

For four days the patient was given 4000 c.c. intravenous fluids daily. There was no urine excretion, no edema or cardiac embarrassment. Cystoscopy on the fourth day in the hospital was done by Dr. Weinstein. The bladder was normal, the ureters easily catheterized, and a few drops of concentrated urine obtained from each. There was no elimination from catheters after irrigation with warm saline solution, no indigo carmine excretion from either kidney. Concentrated glucose was given, but there was no urine excretion.

The patient was becoming more restless and had slight abdominal distention. Dr. Louis Leiter saw the patient on the sixth and seventh hospital day. I saw the patient on the seventh day in consultation and advised immediate wide decapsulation with use of large rubber tubes for drainage and postoperative plasma infusions.

The operation was under novocaine spinal anesthesia supplemented with ethylene gas. Both kidneys were somewhat swollen with smooth, glistening capsules. After complete incision of the capsule, the kidney cortex puffed out. The capsules stripped easily, and cortical biopsies were taken.

[Slide] This is unusual. The stains with the von Kossa stain show these black accretions, in this instance one at the hilus of the glomerulus.

[Slide] Here are the areas in the tubules with some of these concretions between the tubules.

[Slide] Here you see pushing into the tubules; here a concretion, and here apparently a purely acetylated concretion.

This patient recovered very promptly and very satisfactorily and a recent check-up showed normal renal function. The combination of chronic alcoholism, plus sulfathiazole, plus four weeks between the ingestion of the drug and the development of anuria, and then prompt recovery after bilateral decapsulation, I think, is of great interest.

Twelve hours postoperatively, the renal excretion began and increased to 2800 c.c. on the third postoperative day. The blood chemistry was normal on the fifth postoperative day. The convalescence was uneventful and the patient was discharged from the hospital on the sixteenth postoperative day.

The pathological report by Dr. Otto Saphir was: "In a wedge-shaped section through the periphery of the kidney, the cortical tubuli are lined by swollen, frayed and vacuolated cells. Within their lumina are desquamated epithelial cells, occasional red blood cells, basophilic and eosinophilic casts and circumscribed basophilic concretions. The glomeruli are occasionally hyalinized. At the hilus some concretions are noted; with the von Kossa stain, these concretions are black (calcium)."

DR. GEORGE F. CAHILL (New York, N. Y.): I want to discuss two papers, first that by Dr. Howze on diagnosis. Whether a thing is an adrenal tumor or a renal tumor is sometimes very difficult to determine microscopically, and some of these sections look like what we call hypernephroma. It must be done chemically, simply because the adrenal cell and the renal cell are chemically two different things, and long differential chemical staining of cells is the only way. Sometimes it is difficult to determine whether a tumor is of kidney origin with metastasis into the opposite adrenal (which has happened to me), that being the only adrenal present (by autopsy and destruction), with the picture which Dr. Howze has shown. I wouldn't be quite satisfied unless examination pathologically and chemically was made as far as possible to see whether the cells in that tumor are renal cells or adrenal cells.

Dr. Howze's patient naturally died of acute chronic adrenal depletion, chronic Addison's disease; chronic Addison's disease does not need to have pigmentation, because apparently the various syndromes of Addison's disease are also not only loss of hormones but the loss of vitamins which goes with the depletion of an adrenal.

The second discussion is on Dr. Charles McKenna's work on pseudohermaphroditism, which is most extraordinary. These cases are appearing more and more in the literature. Dr. Young blazed the way on that and like the pioneers who go ahead with the torch lighting up the darkness on each side, he had a lot of fun. Now, other men are interested in such a problem because apparently there are a number of these people everywhere who have had nothing done to them previously. Where they were in previous literature is hard to say, considering how many are picked up in the various clinics now.

Dr. McKenna reports the use of air as his diagnostic medium, for which I also am happy, because we have found it of value. Other people, apparently, have been afraid of it or they turned the use of it over to an intern or someone not familiar with the procedure, who produced a tragedy. You can get good results if you don't let just anybody do it.

My experience in what Dr. McKenna has done in cutting down these adrenals is that if you watch them long enough, they are just like thyroid; they are apt to hypertrophy again. The best way to watch them is by their excretion of hormones, although you can

catch them by hair growth, because the most sensitive indicator for male hormone is hair. The most sensitive indicator for female hormone is the nipple. They are two good sensitizing things that you can watch.

We have estimated the actual excretion of male hormone and found they would come back to a certain degree. Taking the clue from Herbst and the men who have used the estrogens, stilbestrol, we have been blocking these things off with stilbestrol and found the clitoris will recede with sufficient therapy and it has not been necessary to take away this particular tragic child's phallus. You can leave the phallus to a certain degree. We hope that sufficient experience may prove to us that we may be able to block the androgenic hormone which is produced by these adrenals, rather than try to do it entirely by surgery, because my experience is that surgery does not complete the job on these people. These things regenerate.

Another consideration is that in all the little children you treat like this—I have had them as young as three, five, seven, nine—you have to block off, too, the finishing of the growth which occurs in their epiphyses. Recent work has shown that all the cortical sterones have something to do with growth determination. We have found clinically that the androgenic one is the most active. But in the laboratory, it is desoxycorticosterone. The life maintenance hormone is the one that apparently accelerates growth faster than the male hormone. In fact, you can give it to rats and instead of opening their eyes on the twelfth day, they will open them on the ninth day, and their teeth become bare on the ninth day, whereas the teeth in the rat don't usually show up until the fourteenth or fifteenth day. But you can step that up with desoxycorticosterone. It is part not only of a change in the sex appearance of the individual, but acceleration of life maintenance goes on. It is a most interesting problem, and I am happy to see that Dr. McKenna has become interested in it, too.

DR. HUGH H. YOUNG (Baltimore, Md.): Dr. McKenna has presented interesting cases of female pseudohermaphroditism. I am glad to see that he has employed our bilateral exposure of the adrenals, with the patient lying upon the chest and abdomen.*

*Young, Hugh H.: Genital Abnormalities, Hermaphroditism and Related Adrenal Diseases. Baltimore: Williams and Wilkins Co., 1937.

There is no denying the fact that it is desirable to expose and examine both adrenals before operating upon either one. The not infrequent absence of one adrenal has shown the danger of removing one adrenal without knowing whether the other was present. The fact that Dr. McKenna was able to remove three-fourths of one adrenal and one-fourth of the other is a strong argument for removing considerable adrenal tissue in these cases of adrenal hyperplasia associated with female pseudohermaphroditism. In my recent cases I usually have removed one adrenal (the larger one) completely, and I think that it may even be desirable to remove perhaps a half of the other. By having an associate operating opposite you, the two adrenals are exposed almost simultaneously, much time is saved, and the operator can then decide what to do on each. In addition to the operation on the adrenals, in most of these cases we have found it desirable to carry out a radical clitorectomy and to go in, free, and bring down to the perineum the undescended vagina. After all this surgery, not infrequently the use of stilbestrol is necessary to develop the breasts into a feminine type and to combat other masculine characteristics. The subject of female pseudohermaphroditism associated with adrenal hyperplasia is one of the most complex subjects from both the standpoint of surgery and endocrinology.*

DR. THOMAS SHUPE (Cleveland, Ohio): I just want to say that I am very glad this question of an aberrant vessel was brought up so that Dr. Young could show that excellent movie of the anterior approach to the kidney pelvis. As we all know, the enlarged kidney pelvis does extend anteriorly more often than posteriorly because of the lessened pressure. It has more room to grow.

I shall certainly use this incision.

DR. CHARLES MCKENNA (Chicago, Ill.): I wish to thank the discussers very much for their remarks. I have read both Dr. Young's and Dr. Cahill's works and they have been a stimulation in our own experiences.

It is interesting to note the changes in these patients after the removal of a section of the adrenal glands. Four important ones are the gradual decrease of hirsutism, breast development, changes

*See footnote, page 59.

in the voice and general body contour from the masculine to feminine.

I am sorry there is not sufficient time to present all our material but it will appear in the Transactions.

DR. YOUNG: Mr. Chairman, may I ask Dr. McKenna how he makes those voice records?

DR. MCKENNA: So far, our only experience has been with the tubular records, such as those in the Dictaphone, which are used by the surgeons for their operative records. The patient uses this same method before the operation and at intervals afterward. The word "fourteen" was used in our cases, and a distinctly higher tone was discernible several weeks after the operation. I believe any recording device could be used for this purpose.

DR. CAHILL: We had these patients sing. They sang the same song and we had it recorded. I think it was "My Country 'Tis of Thee."

Recently a case of pseudo pubertas precox entering the hospital as a boy was found to be a masculinized female without an adrenal tumor. We did not remove the hypertrophied clitoris but used its regression as well as the mammary changes as a yardstick for determination of the dosage of stilbestrol.

WILMS' TUMOR IN THE ADULT

REPORT OF A CASE

GEORGE R. LIVERMORE, M.D.
Memphis, Tennessee

Embryonal (Wilms') tumor of the kidney is essentially a neoplasm of childhood. It does occur in the adult, however, as attested by twenty-six case reports in the literature and by another herewith added by the writer. Crenshaw, in a personal communication, states that there are records of two such cases at the Mayo Clinic.

A Wilms' tumor may be unilateral or bilateral. Sutton says 50 per cent are, or may become, bilateral, but Hinman, in a collected series of 1037, found only 4 per cent were bilateral. A Wilms' tumor usually grows rapidly and is fatal in the majority of cases within one year. Less than 5 per cent are living at the end of five years. Priestley, however, in a series of thirty-nine cases (ages not stated) at the Mayo Clinic, reports a 15 per cent five-year survival record. Metastases are generally by way of the blood stream, the liver and lungs being the usual sites. Involvement of the perirenal tissues by extension from rupture of the capsule may occur in the cases not seen in the early stages. Children from six months to six years seem most predisposed. It occurs with equal frequency in both sexes. Its occurrence in the adult is extremely rare. Unlike most kidney tumors, hematuria and pain are present in only about 10 per cent of cases. Hematuria was not a symptom in my case and there was no pain until a year and a half after the tumor had appeared. The twenty-sixth case was reported by Hamm in the April 1942 issue of *The Journal of Urology*. I now report the twenty-seventh.

There is some controversy as to the value of deep x-ray therapy as a pre-operative procedure in kidney tumors. My patient was given pre-operative deep x-ray with resultant shrinkage and increased motility of the kidney. One swallow does not make a summer but as I have had similar results in other types of kidney tumors (notably hypernephroma) I add this as evidence of its good effect in a case of Wilms' tumor.

Cases in the adult have been reported by Hedren, Jenckel, Kocher and Langhans, Hoisholt, Busse, Dean and Pack, Neff, Priestley, Kilbane and Lester, Nelson, Alcorn, Hasner, Thatcher, Fulmer, Geshickter, Widenhour, Hunt and Hager, and Hamm.

CASE REPORT

Mrs. C. F., aged thirty-seven, white, married, para I. Her father and mother are living and well. The patient was well until her present illness began. Her only child was born in May, 1938. Shortly afterwards she noticed a round, firm non-tender mass in her right loin below the free border of the ribs. This was diagnosed floating kidney and she wore a kidney support until Christmas, 1940, when she had severe right renal colic. An intravenous urogram was made. This showed a kinked right ureter which was thought to be the cause of her colic. She had no more colic but the mass gradually increased in size and there was weight and a dull aching pain in her right loin. There was no macroscopic blood in her urine but a few red blood cells were found on microscopic examination.

In January, 1941, she began having hyperpyrexia; the pain became more severe and the mass was markedly tender on palpation. Her local physician made an exploratory incision on January 15, 1941, and a perirenal abscess and tumor mass were found. The abscess was drained and a biopsy specimen of the tumor obtained. The latter was reported Wilms' tumor.

When first seen by me on June 16, 1941, the wound was still open and discharging mucopurulent material.

Physical examination revealed blood pressure 110/70; heart and lungs negative, teeth and tonsils normal. There was an oval mass as large as a medium sized grapefruit in the right upper quadrant below the free border of the ribs. The mass was firm, round, nonfluctuating and apparently continuous with the right kidney. It was not painful on palpation and was firmly fixed. Her left kidney was not palpable or tender. Red cell count was 4,250,000; hemoglobin 90 per cent, Wassermann negative; leukocytes 8650, polys 77 per cent.

Cystoscopy revealed in the bladder some chronic cystitis. Ureter openings were normal. A No. 5 catheter passed easily to each pelvis; moderate flow, clear urine from left; no flow from right. Indigo carmine appeared on the left in two and one-half minutes, deep in four minutes. There was no dye from the right in thirty minutes. Radiograph showed no stone, but a large mass continuous with the lower pole of the right kidney was seen extending 1 inch below the crest of the ilium. The right ureter was pushed over to the midline of the bodies of the vertebræ. The right pyelogram showed some dilation of the pelvis and calyces. The lower calyx was shortened and the entire pelvis pushed upward. The left pyelogram was normal. The urine

from the left kidney showed 7 plus cells and a few red blood cells to the high power field and staphylococci on culture.

Deep x-ray treatments were begun and continued until July 2, 1941. When seen August 15, 1941, six weeks after the last x-ray treatment, the tumor mass had decreased about 25 per cent in size and was movable. As her red cell count was 4,100,000, and hemoglobin 88 per cent, a transfusion of 500 c.c. of blood was given. Operation

Fig. 1. Right pyelogram.

was performed next day, August 17, 1941. The tumor involved the lower third of the right kidney and was the size of a medium sized grapefruit. The upper two-thirds of the kidney appeared normal but somewhat distorted. Despite the previous operation and the fact that the tumor was adherent to the vena cava for a distance of 3 inches, it was easily freed and removed (although I held my breath when stripping it from the vena cava). The patient made an uneventful recovery and left the hospital on the tenth day.

When I first saw her, on account of the size and fixed position of the tumor, I thought a transperitoneal approach would be necessary.

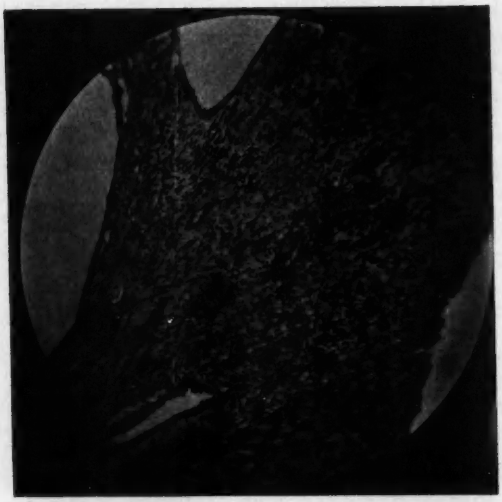

Fig. 2. Photomicrograph 100 X.

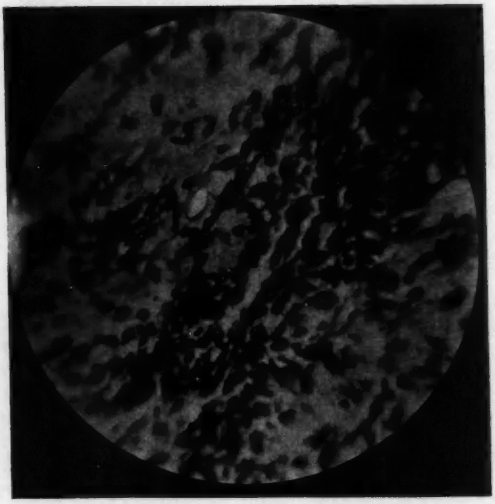

Fig. 3. Photomicrograph 430 X.

Following deep x-ray, however, the tumor diminished in size and became movable; therefore, I used the usual extraperitoneal approach and experienced little difficulty in performing a nephrectomy.

The pathologic report by Dr. N. E. Leake is as follows:

The specimen consisted of the right kidney and tumor mass (which measured 7 cm. in diameter) located in the lower pole. The specimen weighed 355 gm. The tumor mass was soft and friable, yellowish white in color and contained several hemorrhagic cysts. There was some distortion of the upper pole of the kidney but otherwise it appeared normal. The section revealed a myxoid stroma which contained large areas of necrosis. There were masses of spindle and polyhedral cells. There were a number of cells which had the appearance of aborted tubes. In some areas there were a few scattered muscle fibers.

Diagnosis: Wilms' embryonal tumor. This diagnosis was confirmed by the American Urological Association's Carcinoma Registry.

The deep x-ray treatments were administered by Dr. Shields Abernathy. They were begun on June 17, 1941, and ended July 2, 1941. The patient received 4100 R units delivered into the tumor through a 10 cm. cone, two portals, one anterior and one posterior, the factors being as follows: 200 P.K.V., 25 ma. filter 5 mm copper T.S.D. 60 cm.

Treatments were begun at the rate of 250 R per day for two days and then increased to 300 R per day for the rest of the treatment. There was no nausea or other unfavorable symptoms.

The wound was completely healed three weeks after operation and I saw the patient last April 15, 1942, when there was no evidence of a recurrence. She had gained 15 pounds in weight and said she felt in perfect health.

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TUBEROUS SCLEROSIS AND RENAL TUMOR

HENRY O. MERTZ, M.D.

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Prior to this study, the importance of the co-existence of certain diseases of the brain and of the kidney was little appreciated by the author. An instance of tuberous sclerosis of the brain and tumor of the kidney is presented, with the thought that its discussion may be of interest to any who might be similarly uninformed.

Clementine J., a three-year-old, female, white child entered the Riley Hospital in 1934. The complaint was a congenital enlargement of the left leg and of the left side of the vulva. The increase in size had been gradual and progressive since birth.

The patient was born at full term after a normal delivery. She had walked without a limp at the normal age and had never complained of pain or tenderness in the diseased organs. The only evidence of mental retardation observed was some delay in the child's beginning to talk.

The family history was negative for tuberculosis, diabetes, lues, and mental and nervous diseases. The father, mother and two brothers, aged five and six years, were living and well. The patient had had no serious illness and was a well-nourished and well-developed child. Examination of the head and chest was negative. There was some fullness noted in the left side of the upper abdomen. No mass, however, was detected and no attempt was made at this time to determine the cause of this abdominal finding. A marked variation in the size of the two legs was present. The enlargement of the left leg extended from the thigh to the ankle. The swelling seemed to be entirely fleshy, was firm and did not pit on pressure, and no masses were present. There were numerous tiny capillary hemangiomatous areas on the outer aspect of the thigh, and the skin in this region and over the left groin had a slightly bluish tinge. The left inguinal glands were slightly enlarged. There was no limitation of motion of the left leg, and it was only one-half inch longer than the right. The blood pressure in the right leg was 130/80, while the blood pressure could not be determined on the left side. The surface temperature of the two legs was the same. The left labium majus was enlarged, more on its inner aspect, and there were numerous dilated vessels on its surface. These tissues were soft, non-fluctulant, and not tender to pressure.

The urine analysis and blood count were normal. The blood Wassermann was negative.

A diagnosis of probable hemangiomata of the left leg and vulva was made. No treatment was instituted.

The second hospital admission was six years later, when the patient was nine years of age. She entered the hospital because of convulsions, swelling of the left leg and vulva, and a mass in the upper left abdomen.

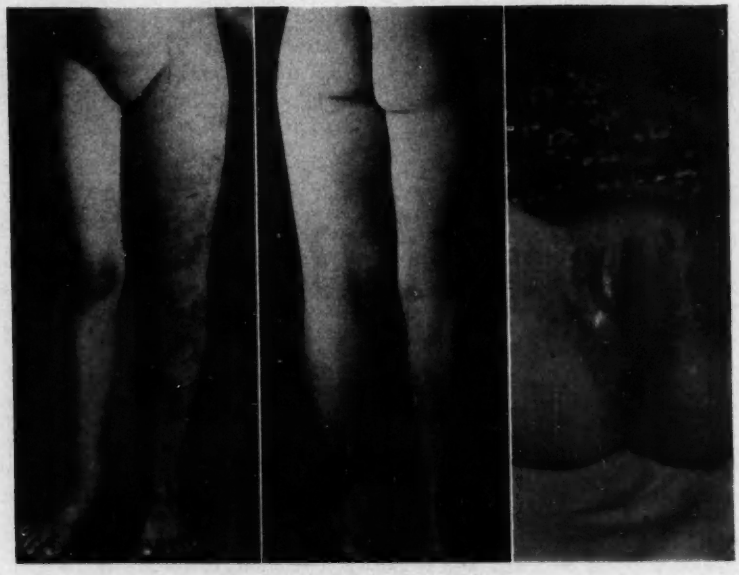

Fig. 1. *(left)* Front view showing increase in the size of the left leg. The angiomatous areas are plainly visible.

Fig. 2. *(center)* Rear view of left leg.

Fig. 3. *(right)* The congenital enlargement of left labium majus. The histologic changes in the swollen leg and labium were studied by Ross in his report of this patient. He referred to these findings as new in the reports of tuberous sclerosis and stated that when encountered they demand a study of the patient for the presence of this disease.

The first convulsion had occurred following convalescence from an infection in the left leg when six years of age. Two weeks following an apparently satisfactory recovery from her leg infection, while standing, she had a typical epileptic seizure. There was no loss of bowel or bladder control during the attack. The convulsions have recurred at irregular intervals since the initial seizure. At one period she had eight convulsions in twenty-four hours. The patient experiences no apparent aura. The attack occurred any time during

the day or night and left the patient with no immediate ill effects as she was soon up and about as usual. The convulsive seizure began in the left side and later involved the right side. Likewise the head was first thrown to the left side. The attacks seemed to have no causal relation to the normal body functions.

Physical examination elicited no paralysis or ataxia of the extremi-

Fig 4. The typical skin lesion present is shown here. A discussion of the various skin manifestations of tuberous sclerosis is given in detail by Ross in his study of this patient.

ties. The reflexes of the lower extremities were appreciably lowered. The child's mentality was low, falling into the moron group. Her progress in school was slow and she was compelled to quit school because of her convulsions.

A skin eruption was present over the face. This consisted of a fine reddish maculopapular lesion of about 1 mm. in diameter, which had a butterfly distribution over the cheeks and nose. The eruption also was present on the chin. The lesions were somewhat more coarse in the nasolabial folds. In addition to these, there were situated on the upper eyelid and forehead, two brownish, slightly raised

lesions 5 mm. in diameter. On the right lower abdominal region and over the back were scattered faun colored, slightly elevated flat patches, varying in size from 1 to 6 cm. (Fig 4).

Ophthalmoscopy showed the disk margin blurred with some hyperemia. The vein-artery ratio was normal. There were no findings suggesting von Hippel's disease.

The left leg was approximately one and one-half times as large as

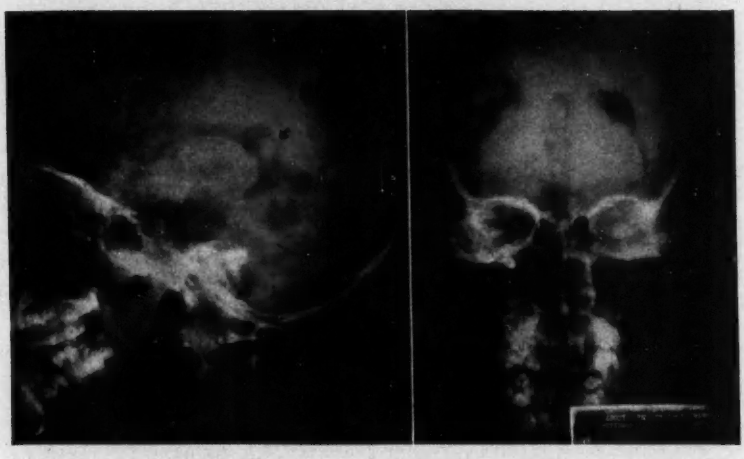

Fig. 5. *(left)* Ventriculograms demonstrating rounded filling defects (arrow) about 1 cm. in diameter in the posterior portion of the body of the right lateral ventricle. This is considered due to the presence of a subependymal tumor. The second arrow in the lateral projection indicates the largest of several areas of sclerosis in the cranial bones.

Fig. 6. *(right)* Anteroposterior view of skull after injection of the ventricles.

the right, and the left labium majus was definitely hypertrophied (Figs. 1, 2 and 3).

In the upper left abdominal quadrant was a mass the size of a grapefruit. It extended under the ribs above and reached the midline of the abdomen in front. Its lower border was on a level with the umbilicus. The mass moved with respiration, was not tender to palpation, and it had an almost smooth surface. This was diagnosed by pyelography as a renal tumor. There had been no clinical symptoms caused by this tumor of the left kidney, and the urine was negative. (Figs. 7, 8 and 9).

X-ray studies of the skull by means of the encephalogram revealed the entire ventricular system to be well outlined with air. There were multiple irregular areas of calcification which appeared to be within the substance of either the inner table of the calvarium or the

Fig. 7 Fig. 8 Fig. 9

Fig. 7. Intravenous pyelograms showed satisfactory visualization of the right kidney. The pattern outline of the pelvis indicated an abnormally long superior major calyx, with irregular cupping. This retrograde pyelogram indicates the same variations from the normal. These may be evidence of the typical changes accompanying tuberous sclerosis or but a congenital variation, tending to result in a bifid pelvis.

Fig. 8. The intravenous pyelogram resulted in but blotches of the dye scattered throughout the left renal area. The density of these areas was equal to that on the right side, although the outline of the pelvis was not complete. The retrograde left anteroposterior pyelogram is shown here indicating the presence of a left renal tumor deformity.

Fig. 9. The retrograde left lateral pyelogram when compared with Figure 8 indicates the degree of displacement of the kidney and deformity of the left kidney pelvis.

cortical surfaces of the cerebral hemispheres. These were chiefly present over the vertex. In addition a rounded defect of increased density, measuring about 1 cm. in diameter, appeared to be lying within the posterior portion of the left lateral ventricle near its junction with the occipital horn. There was some anterior protrusion of this lesion into the ventricle, with some local dilatation of the ventricle immediately about it, suggesting that it might actually be a subependymal lesion (Figs. 5 and 6).

Impression: The irregular areas of increased density in the calvaria or cortical surfaces of the brain together with the nodular lesion in the posterior portion of the left lateral ventricle were pathologic changes most probably due to a tuberous sclerosis.

While not present in this patient osseous changes in tuberous sclerosis may occur in the bones of the extremities where there will be areas of cortical thickening with overlying periosteal proliferation and calcification which is also usually associated with some cystic-like areas of varying extent and size within the cancellous and spongiosal portions of the shafts of the bones.

A diagnosis of tuberous sclerosis with adenoma sebaceum, left renal tumor, and congenital angiomatous changes in the left leg and left labium majus was made.*

The patient was placed upon sedation treatment for her convulsions, and x-ray treatment for her renal neoplasm.

DISCUSSION

The three types of neurocutaneous syndromes most often encountered, which may be accompanied by a renal tumor, are Recklinghausen's neurofibromatosis,[22] Bourneville's tuberous sclerosis[3,16] and Lindau's type of von Hippel's disease, an angiomatosis. Each is due to a congenital malformation occurring in the brain, skin, heart, eyes, kidneys, bones, and occasionally other viscera. The pathologic changes and the clinical expression are distinctive and definite in each disease. However, there may be an overlapping of the morbid process when the clinical findings will be confusing, or a frustrated form of the disease may exist when symptoms ordinarily present will be absent. While knowledge enabling an accurate differential neurologic diagnosis of these diseases is not demanded of the urologist, he should be sufficiently informed

*The diagnosis of tuberous sclerosis was made by Dr. A. T. Ross, who referred the patient to us for study of the abdominal mass. The clinical notes are taken from the hospital record, as written by Dr. Ross, and from his report of the case in the *Quarterly Bulletin, Indiana University Medical Center*, 3:13, (January) 1941.

I wish to express my appreciation to Dr. Ross and Dr. David A. Boyd of the Department of Mental and Nervous Diseases, to Dr. Arthur Echternacht of the X-ray Department, and to Dr. Clyde Culbertson of the Department of Pathology for their assistance in reporting this case.

so that he will recognize the possible presence of any one of them in a given clinical case, and know of the tendency towards developmental renal changes in that patient. The following discussion is limited to tuberous sclerosis, the disease of the group which is the most clear cut both as to the pathologic changes and the clinical symptoms present.

Tuberous sclerosis is a chronic disease which particularly affects the brain, eyes and skin, but which to a lesser degree involves the mesoderm, resulting in embryonic tumor formation in the heart, kidney and other viscera. Invasion of the brain results in varying degrees of mental defect and convulsions. The skin lesion, adenoma sebaceum, is present on the cheeks and nose. It is most characteristic in its butterfly distribution and is usually most evident in the nasolabial folds. The eye changes consist of flat tumors on the retinæ.[20] Typical changes occur in the heart and kidneys and less frequently in other viscera. The syndrome of mental deficiency, convulsions, and adenoma sebaceum is called epiloia (Sherlock).[17] There are other less constant, but possible symptoms and signs of the disease, which should be understood by the urologist. These are important as the clinical picture of the disease may not be complete due either to an abortive or atypical form of the disease or to the age of the patient, when in the latter instance there may not as yet have been sufficient time for full development of the entire syndrome. The very young patient may have an apparently normal mentality for his age, and convulsive seizures may be absent, but there may be present various nervous attacks involving crying and screaming as the sole complaint. However, some degree of abnormal mentality most often will be present, varying from mildest imbecility to complete idiocy. Delayed walking, talking and dentition are frequent complaints.

The diagnosis of tuberous sclerosis without a skin lesion is infrequent. However, this finding may not be present in the infant or young child, as in our patient adenoma sebaceum was noted as being present only upon her second admission. That this skin change may develop up to the time of puberty, seldom later in life, vitiates in a large measure the value of the absence of this lesion in eliminating tuberous sclerosis in these young patients. Eye changes also may be absent. Various congenital defects and anatomic stigmata, however, frequently accompany tuberous scler-

osis and these assume an added importance when co-existing with a renal tumor. These are harelip, cleft palate, high arched palate (this deformity is frequently mentioned), hypertrophy of the ears, peri-ungual and subungual warts, simian hands, accessory digits, hemihypertrophy and spina bifida. Other malformations may co-exist with less frequency. Likewise scattered fibromata on the body and discolored patches of the skin may accompany this disease. While ophthalmoscopic examination is not regularly as informing in tuberous sclerosis as in Lindau's type of von Hippel's disease, it should not be omitted when tuberous sclerosis is suspected as occasionally there may be seen in the retina a "duplicate of the process which is developing in the brain." The disease has a familial tendency and has been reported present in several members of different generations of the same family. Thus a patient with a kidney tumor and with one or more of the symptoms or findings as noted above should have the advantage of a neurologic and psychometric survey and of an ophthalmologic and dermatologic consultation before the surgical removal of the kidney is undertaken.

There is no treatment known for tuberous sclerosis at present. It has a progressively downward course. It is observed in adulthood but occurs most often in children. Most patients die between the fifth and fifteenth years of age and death results most often from cachexia, pulmonary disease or status epilepticus. However, in Fowler and Dickson's[8] report of twenty-nine cases, three died of the renal disease. (Vogt, Case 1 and Case 2 and Bonfigli, Case 2). In their series, two died before five years of age and twenty had died by the sixteenth year.

The characteristic kidney lesion in tuberous sclerosis is a tumor formation. It is interesting that Bourneville, in his report of his first case in 1880, noted the presence of renal tumor and this association was so constant in his subsequent cases that he was soon led to observe, "We must bear in mind the small neoplasms of the kidney, lesions which are constant in the disease." While their presence was at first thought to be accidental and had no relation to the brain lesion it was soon suggested that the renal changes had more than a casual relationship and that the hypertrophic nodular gliosis in the brain, and the tumor formation in the kidney, were but two expressions of one and the same disease. Ja-

cobæus,[13] in 1903, and Vogt,[21] in 1908 to 1910, emphasized that the brain, skin and visceral changes were similar in nature and constituted but different lesions of an identical disease. Kirpieznik,[15] in 1910, Fischer,[7] in 1911, and Hyman,[12] in 1922, are among those who have chosen to emphasize the kidney lesion in their articles.

Most of the complete autopsy reports of patients with tuberous sclerosis have noted the presence of renal tumors, yet occasionally an instance of tuberous sclerosis without kidney changes has been shown. Thus in Sailer's[18] series of thirty cases of the disease, two —those of Hartigan and Spiller—had no renal tumor. In Fowler and Dickson's series of twenty-nine cases in only one, Bourneville's case, were the kidneys reported normal. In Critchley and Earl's[5] four patients who had autopsies, the characteristic renal changes were present in each. The renal tumor is relatively more frequent in tuberous sclerosis than is tumor of the heart, and the two lesions may co-exist in the same individual as was indicated by Furber's[10] studies. In his series of twenty-five instances of definite tuberous sclerosis and rhabdomyomata of the heart it was stated that in only two renal tumors were not present, the observations of von Recklinghausen and Abricassoff. Hyman concluded that 80 per cent of the patients with tuberous sclerosis had renal tumor, and Fischer in his study states such renal lesions are probably present in about all cases.

The renal changes may be bilateral. The relative frequency of both kidneys being involved is difficult to determine as reference to the renal lesion in autopsy reports is most often limited and incomplete. In sixteen of the nineteen cases of renal tumor in Fowler and Dickson's series, both kidneys were affected. In Critchley's and Earl's four cases the kidney lesion was bilateral in each, and they conclude that "usually both kidneys are involved."

In the series of forty-two patients with tuberous sclerosis and tumor of the kidney, the records of whom I have collected from the literature, the disease was bilateral in thirty-four and stated to be unilateral in two. No statement was made in the remainder. The postoperative clinical course of the patients of Hyman and Froug[9] would suggest the lesion was unilateral or that the invasion of the remaining kidney was insufficient to seriously handicap

its function at the time of operation. Kirpicznick's patient with tuberous sclerosis and renal tumor died following a right nephrectomy undertaken because of right renal pain and tumor mass. The autopsy disclosed tumors in the left kidney and Kirpicznick made a careful histologic study of this kidney. It is interesting to note that this patient's father died following a nephrectomy. Likewise Berg[1] reports an instance of the death of a man after a renal operation and an autopsy disclosed a tumor was present in the remaining kidney. The child and grandfather of this man each had tuberous sclerosis and renal tumors.

The kidney changes accompanying tuberous sclerosis have received but indifferent attention when compared to the detailed study made of the lesions of the brain and skin. The characteristic lesion is a cystic or solid tumor. While these may occur independently, careful study in most instances will demonstrate both types of tumor present. The tumors are primarily cortical in location and they frequently will extend into the medulla, but in doing so there is no invasion of the deeper structures as in malignant renal tumors. Almost invariably the tumors are multiple and many definitely distinct tumors are present with no appreciable tendency toward the formation of one large tumor mass. The histologic structure of these tumors has been studied in great detail by Fischer. His material consisted of the kidneys from eight patients who had histologic and clinical evidences of tuberous sclerosis of the brain. His conclusions were much as follows:

Cysts were present in all kidneys studied. These were multiple and co-existed with the solid tumors of the kidney. The cysts were thin-walled and were filled with a homogeneous glassy content which contained no fat. They were most often lined with a single layer of epithelium. They varied in wide limits in size and were identical in their histologic structures regardless of size. He concludes these cysts are congenital and are an evidence of a disturbance in the development of the kidney.

Attempts to classify the solid tissue changes in the vast majority of the patients reported have been limited to an identification of the predominating type of tissue present. Thus a great many different names have been given to these renal tumors found in individual patients who had tuberous sclerosis: Gavazzeni[11] reported an angiomyofibroma; Jacobus,[14] an angiomyosarcoma; Vogt

and Froug, a liposarcoma; Bonfigli,[2] a fibrosarcoma; Fischer-Volland, a lipomyosarcoma; Campbell,[4] an endothelioma; Critchley and Earl, a perithelioma and mixed sarcoma, et cetera. Most observers were inclined to consider the findings in their patients as an evidence of changes indicating various stages of the usual renal tumor observed in children. However, among these data appears the diagnosis of hypernephroma (deMontet,[6] Marcuss,[17] Bonfigli, and more recently Hyman). That the characteristic renal change in tuberous sclerosis is ever hypernephroid in nature seems very doubtful, and Fischer states, "This tumor has in no particular a resemblance to hypernephroma." In none of the detailed autopsy reports have I found description of a typical hypernephroma occurring in tuberous sclerosis. Lindau noted that the cells of a hemangioblastoma occurring in certain types of von Hippel's disease may closely resemble those of a hypernephroma, and cites an instance when such a metastatic tumor was at first thought to be secondary to a primary hypernephroma, which, however, did not exist. The frequent parallelism in the clinical syndrome of this disease and tuberous sclerosis might conceivably cause confusion in the rare patient in identifying the nature of the renal tumor present.

Fischer's studies showed the characteristic solid renal tumor of tuberous sclerosis, regardless of its size, consisted of fat, smooth muscles, and capillaries and arteries. These differed much in relative quantity in individual tumors and in different portions of the same tumor, but were always present. The tumors were situated in between perfectly normal kidney tissue, never showing a tendency to invade the surrounding renal tissue, the two being distinctly separated. The arteries were usually more evident than were the capillaries. The vessels showed thickening of the media and adventitia. Some vessels were fully developed while others were young and immature. In no instance did the tumor exist exclusively of such vessels but always both fat and muscle were present.

The fatty tissue was usually fully developed. Isolated clumps of fat cells were at times found within kidney substance where the other two types of tissue were absent, but in most instances it was accompanied by muscles and vascular channels. The smooth muscle fibers, as a rule, were well developed, although young muscle cells were at times present. No striated muscle cells or carti-

lage were found in any of these kidneys. The connective tissue septa were poor in nuclei and oftentimes deposits of lime were found in this tissue.

In addition to these tissues, rarely were clumps of epithelial cells present. These in some areas were inclined to be glandular in arrangement and in others they showed a tubularlike formation. Very rarely did such areas exist at all.

There was no evidence of small cell infiltration and no apparent tendency for necrosis of the diseased tissue, although this did occur in one of Critchley and Earl's patients and in Hyman's patient. There was no inflammatory reaction between the foci and normal kidney tissue.

From these data Fischer concludes the lesion is characteristic for this disease; that it is congenital and shows no evidences of any relation to an inflammatory process. It is benign as it does not invade the surrounding renal tissue in the midst of which it it situated, nor does it extend beyond the renal capsule although it may project upon the surface of the kidney for varying distances depending upon its size.

This tumor differs histologically from Wilms' tumor in that it does not contain striped muscle or cartilage; that epithelial elements in the foci are rare; that calcification does occur; that there is no tendency to invade normal kidney tissue nor extend beyond the capsule; that it does not metastasize; that the lesions are multiple; that there is no evidence of the coalescence of the individual foci into one large tumor mass, and the lesions are in most instances bilateral. Clinically these tumors differ from Wilms' tumor in their slow growth and in the absence of the usual clinical evidences of the neoplasm. Finally, death is very rarely due to the renal lesion.

That the tumor may grow to large size is indicated by the findings in our patient. When symptoms result because of the size of the tumor, pain or a co-existing infection, surgical intervention may be demanded. In the absence of symptoms and where only the existence of a tumor mass draws attention to the urinary tract, the real lesion should be dealt with conservatively. In our patient all treatment has been limited to irradiation of the growth. Apparently the growth is radioresistant in this patient as

one series of twenty treatments has not appreciably lessened the size of the growth.

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CLINICAL PERINEPHRITIS AND ITS EFFECT ON BLOOD PRESSURE

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The production of experimental arterial hypertension by cellophane perinephritis has suggested the question whether clinical perinephritis may be an etiologic factor in hypertension of human beings. Cellophane perinephritis as produced by Page is obtained by the loose application of a layer of cellophane about the kidney. Cellophane excites a marked tissue reaction characterized by the production of a fibrocollagenous hull which appears in a period of two to three weeks and which surrounds and compresses the renal substance. Graef and Page have demonstrated evidence of this compression in the form of areas of focal cortical and tubular scarring of the ischemic type. Usually, after an interval of three to five weeks arterial blood pressure increases markedly; the pressure continues to be sharply increased for a short time and then levels off and remains at a more or less constantly elevated level. In those animals in which only one kidney is so treated and the opposite kidney is intact, the increase in blood pressure is less pronounced and less stabile; the blood pressure tends to subside gradually to normal or nearly normal levels, although a few animals maintain a persistently increased blood pressure.[6] In a few of the animals, however, the increase in blood pressure appeared so early in the course of the perinephritis that the exertion of pressure by the incompletely organized fibrocollagenous hull did not seem probable and morphologic evidence of ischemia of the renal substance could not be demonstrated.[5]

It occurred to us that perhaps a survey of the records of cases of perinephric abscess observed at the Mayo Clinic might cast some light on the clinical phase of this problem. In a recent paper by Walters, Hammer, and one of us (W.F.B.)[2] the opinion had been expressed that acute cortical renal infection or perinephritic abscess was not a common etiologic factor in hypertension.

CLINICAL STUDY

A group of seventy cases were selected from the clinical records during the eleven-year period of January, 1930, to December, 1940, inclusive in which a positive or presumptive diagnosis of primary perinephritis or perinephritic (perinephric, perirenal) abscess had been made. In a number of cases acute cortical renal infection probably preceded the perinephritis. However, with only two exceptions, all cases in which there was evidence of other primary renal lesions, such as lithiasis, hydronephrosis, pyonephrosis, pyelonephritis, tuberculosis, neoplasm, polycystic disease, and so forth, were excluded. Of the seventy patients whose records were studied, fifty-two were men and eighteen were women, a ratio of 2.89:1. The mean age for the

TABLE I. AGE AND SEX OF PATIENTS WITH PERINEPHRITIS

Age years	Total	Males	Females
0– 9	1	0	1
10–19	7	6	1
20–29	7	6	1
30–39	26	20	6
40–49	16	11	5
50–59	7	4	3
60–69	6	5	1
Total	70	52	18
Mean age	38.3	37.4	40.9

group was 38.3 years. Eighty-one and four-tenths per cent of the group were less than fifty years of age. The age and sex distribution in decades is given in Table I. In sixty-seven of the cases the diagnosis was verified through surgical exploration; in the three remaining cases the clinical and urographic evidence was sufficient to warrant the diagnosis, although the treatment was conservative.

The blood pressures used for the study were those recorded dur-

ing the initial clinical examination of the patient. As in previous publications from the Mayo Clinic on renal disease and hypertension, a patient was considered to have hypertension if the systolic blood pressure was equal to or exceeded 145 mm. of mercury, or the diastolic blood pressure was 90 mm. or more.[1,2] The systolic and diastolic blood pressures are given in Table II.

TABLE II. BLOOD PRESSURE IN SEVENTY CASES OF PERINEPHRITIS STUDIED

Blood pressure mm. of mercury	Cases	Blood pressure mm. of mercury	Cases
Systolic Blood Pressure			
90– 99	6	140–149	3
100–109	10	150–159	1
110–119	27	160–169	1
120–129	15	170–179	0
130–139	6	180–189	1
Diastolic Blood Pressure			
50– 59	1	80– 89	20
60– 69	16	90– 99	4
70– 79	28	100–109	1

Analysis of the group revealed that six patients could be classed as hypertensive by virtue of elevation of the systolic and/or diastolic blood pressures. This is an incidence of 8.6 per cent. In two of these six cases, however, conclusive evidence was present that hypertension had existed prior to onset of the perirenal disease. One of these patients had known for twenty years that he had hypertension; the other, for at least two years. In a third case other factors apparently were operating to influence the arterial blood pressure and, although the blood pressure was 114 mm. of mercury systolic and 90 mm. diastolic at the time of drainage of the perirenal abscess, one year later it had increased to 148 mm. systolic and 90 diastolic. Thus only three cases remain in which association between perinephritis and elevated arterial

blood pressure might be present, an incidence of but 4.3 per cent. The possibility of a chronic diffuse cicatricial process in the kidneys was not revealed by ordinary tests. This possibility may be of importance.

It is of some interest to consider individually the three cases which might be interpreted as indicating some association between perirenal inflammation and increased arterial blood pressure.

Case 1.—The patient, a man aged fifty-four years, gave a history of right renal injury five months prior to registration at the clinic. During the interval between the injury and registration he had suffered from recurrent attacks of pain in the right flank associated with occasional fever and chills. Clinical study suggested the presence of bilateral renal infection and evidence of pyonephrosis in the previously damaged right kidney. His blood pressure was 148 mm. of mercury systolic and 90 diastolic. Surgical exploration revealed obliteration of the right renal capsule by old scar tissue; the kidney could be identified only by incision of this densely scarred capsular tissue. Nephrectomy was performed because of marked destruction of the substance of the right kidney.

Seven months later the patient's blood pressure was 145 mm. systolic and 80 mm. diastolic, and three years later it had risen to 170 mm. systolic and 102 diastolic.

Comment.—It will be noted that the blood pressure was reduced somewhat after the operation. The later increase may have been the result of infection in the left kidney. On the other hand, the blood pressure prior to the renal trauma was not recorded and a predisposition to hypertension cannot be excluded on the evidence available.

Case 2.—The patient, a man aged forty-five years, had suffered from pain in the left flank for six months and chills and fever for one month prior to registration. Clinical evidence pointed to the diagnosis of left perinephritis and surgical exploration revealed marked edema and induration of the perirenal tissues with formation of a thickened wall about 2 cm. in diameter around the kidney. Incision of this thickened wall released a large quantity of seropurulent fluid. The kidney seemed normal on palpation and was not disturbed further.

Prior to operation the blood pressure was recorded as 138 mm. systolic and 90 diastolic. Unfortunately, no postoperative values for blood pressure were recorded and thus we do not have any indication of any positive or negative effects. The fact that the kidney was subjected to pressure is indicated by the encapsulated fluid around it as well as urographic evidence of medial displacement, but conclusions cannot be drawn concerning association of this pressure with the minimal increase in arterial blood pressure.

Case 3.—The patient, a white man aged forty-five years, had suffered from right costovertebral pain, fever, and malaise for four weeks. His blood pressure on admission to the clinic was 150 mm. of mercury systolic and 108 mm. diastolic. Urographic studies were not made. A large right perinephritic abscess was drained of about 1 pint (500 c.c.) of pus. On a subsequent visit to the clinic, one year later, the blood pressure was 98 mm. systolic and 60 diastolic.

Comment.—This is a striking example of the result which can be expected if the experimental and the clinical findings are parallel. There is no other evident way to account for the reduction in blood pressure.

Extent and Duration of Perinephritis.—The surgeon's dictation in each of the sixty-seven cases in which operation was performed was reviewed in an effort to gain some idea of the extent of the perinephritis and thus some estimate of the pressure that may have been exerted on the involved kidney. In most instances some description of the amount of edema and induration of the perirenal tissues or of the quantity of pus released from the abscess cavity was given. In those cases in which a collection of purulent fluid was found, the average quantity was in the neighborhood of 10 to 14 ounces (300 to 420 c.c.), although the range was from as little as an ounce (30 c.c.) to several quarts (about 3,000 c.c.). Lest such quantities of pus seem excessive, it must be emphasized that the majority of these patients were not seen by us until relatively late in the course of the disease.

In a number of cases the character and extent of the perinephritis seemed to resemble the experimental type rather closely. In one case, an infiltrated region of stony hardness surrounding the kidney was noted. In another, much inflammation of the entire renal capsule was present with induration which extended down through the pelvis and behind the ureter. In a third case, the entire renal region was involved in almost cartilaginous scar tissue and there were many collections of inspissated pus which made it impossible to determine the condition of the kidney and its capsule. In a fourth case, the renal capsule was at least 3 to 4 cm. thick in places, with an average thickness of 2.5 cm.; this thickness was due to a chronic inflammatory reaction. In no one of these cases was blood pressure increased.

Urographic evidence of marked medial or lateral renal displacement, or of deformity of the renal pelvis or calyces resulting

from extrarenal pressure, used as an index of pressure exerted upon the substance of the kidney, did not exhibit correlation with any increase in blood pressure.

The approximate duration of disease as roughly estimated from the time of onset of presumptive symptoms until registration at

TABLE III. APPROXIMATE DURATION OF SYMPTOMS* IN CASES OF PERINEPHRITIS STUDIED

Duration of symptoms, weeks	Cases
1	6
2	10
3	5
4	15
5	2
6	4
7	—
8	10
8 wks. to 1 yr.	14
1 to 2 yrs.	2
5 yrs.	1
Indefinite †	1
Total	70

*Onset of presumptive symptoms to time of diagnosis.
†Long, vague story of lower abdominal distress without definite time of onset elicited.

the clinic is given in Table III. It is readily seen from this that in approximately 50 per cent of the cases the symptoms of perinephritis had been present for one month or less, and in the remaining 50 per cent the symptoms had been present for from one month to five years. Thus we can say that in at least half of the group the renal lesion had progressed to the stage of chronicity when the patient was seen first at the clinic. On this basis,

if any parallel existed between clinical and experimental perinephritis, hypertension would have been established in at least a reasonable percentage of the cases.

Additional Records Studied.—As a matter of interest, the records in a group of cases of perinephritis secondary to some primary renal disease, such as renal lithiasis or hydronephrosis or both, or pyonephrosis, were reviewed for evidence of association of elevated blood pressure. The cases in this group were selected according to the degree of perinephritis present, the blood pressure being ignored until the group analysis was begun. In twenty-eight cases the perinephritic reaction was considered to be of sufficient degree to warrant inclusion in this group. In six (21.4 per cent) of these twenty-eight cases, hypertension was present. This figure cannot be correlated with that for the group in which primary perinephritis was present by reason of the added factors of chronic renal infection, lithiasis or ureteral obstruction. However, Walters, Hammer, and one of us (W.F.B.) previously had noted hypertension in 22.5 per cent of cases in which renal stone was complicated by infection.

Blood Pressure at Time of Subsequent Examinations.—Of the original group of seventy patients, twenty were reëxamined at the clinic at some time subsequent to the treatment for perinephritis. Analysis of the blood pressures recorded on these subsequent visits revealed that in two cases in which the blood pressures previously had been normal, hypertension had appeared during the interval between examinations. In one of these, our records indicated that the blood pressure had not increased until more than six years after drainage of the perinephritic abscess, and in the other the involved kidney had been removed at the time of treatment of the perinephritis. Conversely, four patients had blood pressures which were reduced from their previous levels. One of these (Case 3) has been discussed. Another had marked pyelonephritis, perinephritis and, in addition, hypertension prior to the perinephritis. Nephrectomy was performed. In the remaining two cases, the blood pressures had always been within normal limits and the amount of reduction was too slight to be considered of any significance.

COMMENT

The foregoing evidence indicates that clinical perinephritis and arterial hypertension are not associated to any significant degree. It is possible, of course, that there is a phase of hypertension, associated with the progress of clinical perinephritis, which has escaped us, inasmuch as experimental hypertension appearing after unilateral renal ischemia or unilateral cellophane perinephritis is less marked and usually of a temporary nature, when the contralateral kidney is normal.[4,6] Page has shown that experimental hypertension usually appears in three to five weeks' time and then, over a period of six weeks, the blood pressure gradually subsides to normal or nearly normal levels. It is our opinion, however, that these factors have been balanced both by the size of the group and by the wide spread in the duration of the perinephritis.

We realize that, in most instances, clinical perinephritis cannot be compared, on an anatomic basis, with cellophane perinephritis, the latter being a highly specialized entity. However, we do find a number of cases in which the state of the perirenal tissues must have nearly approximated the state in the experimental perinephritis.

Included in our group was one case in which a solitary kidney was involved by a marked perirenal inflammation. Left nephrectomy, for nephrolithiasis, had been done elsewhere one year previous to the onset of the perinephritis. On examination at the clinic the patient gave a history of pain in the right flank, chills, and fever, over a period of fifteen days. Her blood pressure was 120 mm. of mercury systolic and 74 diastolic. At surgical exploration marked perinephritis was noted and incision of the renal capsule released 800 to 900 c.c. of purulent fluid. In this case then we had the elements of inflammation and pressure in a solitary kidney. Hypertension was not present, although the duration of infection was more than fifteen days, and it might logically be supposed that it would have made its appearance. This, however, is but an isolated instance and we are not justified in drawing any conclusions from it.

We might theorize that, in comparison with the experimental animal, the normal kidney of man has a greater ability for production of inhibitor substance to counteract the increased produc-

tion of pressor substance by the involved kidney. Clinical practice does not permit an answer to this as yet, although Corcoran and co-workers[3] have demonstrated that the renal pressor effects of infusions of angiotonin on human beings closely parallel those exhibited by the experimental animal.

SUMMARY AND CONCLUSIONS

A group of seventy cases of clinical perinephritis has been analyzed for evidence of association with arterial hypertension. Some correlation between hypertension and perinephritis was found in only 4.28 per cent of the group. This is less than half of the incidence of hypertension existing in a random sample of patients less than fifty years of age who register at the Mayo Clinic and, in our opinion, it is so low that it should be relegated almost entirely to chance.

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ADENOMA OF THE KIDNEY WITH ASSOCIATED LESIONS

REPORT OF THREE CASES

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In 1895 Sturm distinguished between the solitary adenoma of normal kidneys and multiple adenomas of sclerotic kidneys. He was of the opinion that adenomas change slowly into carcinoma. Sebourin, in 1887, described two forms of multiple adenomas, those lined with cylindrical and those with cuboidal cells. Adami, in 1909, in his classification divides renal tumors into epithelial, connective tissue and mixed types; the epithelial tumors comprising adenoma and carcinoma. The relative frequency of different types of renal tumors is difficult to ascertain because of the great difference of opinion in the classification of these tumors.

Adenoma of the kidney is usually small and may be single or multiple; it may be grayish or yellow in color and appears in the cortex just beneath the capsule as in the first two cases here reported. Large adenomas, as in the third case, are exceedingly rare. Kretschmer and Doehring, reviewing the literature to 1929, found but seventeen cases, to which they added one of their own. Since 1929 cases of large adenoma of the kidney have been reported by Bailey and Harrison, Bourque, Char, Dukes, Gordon-Taylor and Manning, although there have been numerous articles concerning small multiple adenomas; the bibliography from 1929 to date is appended.

It is generally acknowledged that adenomas of the kidney are essentially benign but the dividing line between normal epithelium and adenoma, or adenoma and carcinoma may often be difficult to define. The small, often multiple adenomas are sharply demarcated and consist of a mass of small tubules packed closely together, showing no glomeruli. A part or all of the cells may be arranged in groups which have no lumina, or the ducts may be dilated and show epithelial hyperplasia or papillary projections. In another type designated as alveolar, the pattern may simulate adrenal rests, a fact which has given rise to much discussion as to its pathogenesis. In this type the cells are cuboidal or cylin-

drical, may be granular and free of fat, or they may contain a large amount of fat. The small adenomas are often found at autopsy but as they become larger, they frequently show changes which render a differentiation from malignancy quite impossible in some instances.

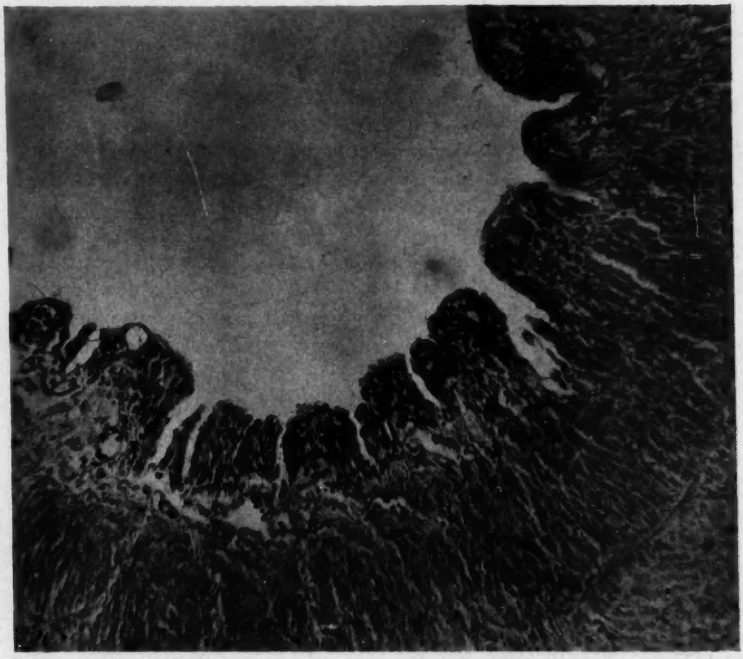

Fig. 1. Lining epithelium of pelvis of kidney showing vacuolated and hyperplastic areas accompanying a hydronephrosis.

The theory that adenomas develop in sclerotic kidneys, often in association with cysts, seems to be borne out in the cases studied in this report, as in two instances the adenomas were associated with advanced sclerotic changes, one a hydronephrosis and the second a pyonephrosis with calculi. In another case of hydronephrosis, sections of the lining epithelium showed vacuolated and hyperplastic areas which, while not definitely forming an adenomatous tumor, still showed an epithelial proliferation which

was in all probability the beginning of a neoplasm (Fig. 1), while in still another case a massive adenoma of the alveolar type was present with an associated tuberculosis.

Case 1.—A man, forty-three years of age, gave a history of pain in the left flank twenty years before, which lasted three days. He had no associated symptoms and the pain recurred at approximately monthly intervals for about two years. He consulted several physicians. The

Fig. 2. *(left)* Case 1. Retrograde ureterogram. Fluid does not enter the pelvis.

Fig. 3. *(right)* Case 1. Excretory urogram showing increased size of left kidney with normal function of right kidney.

presence of a renal calculus was suspected, but repeated radiographs showed no abnormality. No cystoscopic examination was made.

A subsequent attack in 1928 was readily relieved and radiographs again gave negative findings. During 1933 and again in 1938 the patient had attacks of pneumonia. On October 23, 1940, he began to have a gradually increasing pain in the left flank which did not radiate and subsided within twelve hours. Since then to the time of admission to St. Luke's Hospital on October 28, 1940, a soreness in the left loin persisted. He had no gastrointestinal symptoms, no urinary symptoms —urinalysis was negative. Blood chemistry and blood counts were normal. General physical examination gave negative findings, aside

from an indefinite sense of fullness in the left upper quadrant and left flank. Blood pressure was 126/60.

On cystoscopic examination a ureteral catheter passed 9 cm. in the left ureter but was then arrested by a spasm of the ureter. A ureterogram showed that the diodrast did not enter the kidney pelvis (Fig. 2). An excretory urogram was then made which revealed a large indefinite left kidney shadow (Fig. 3) which was interpreted to be a hydrone-

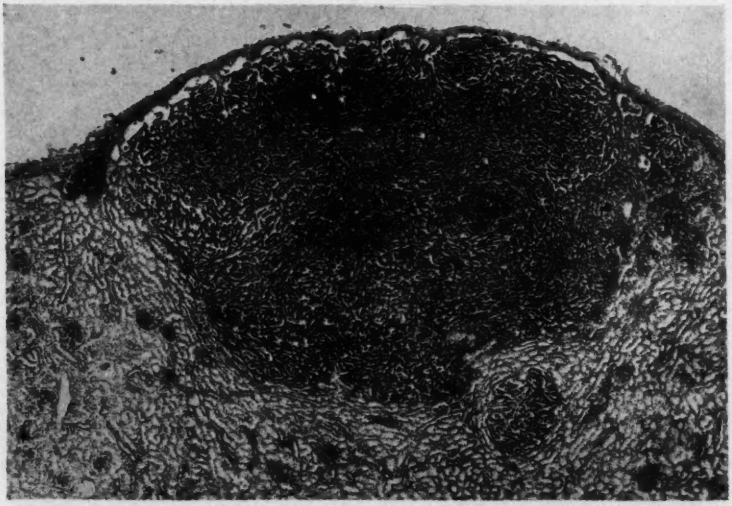

Fig. 4. Case 1. Papillary adenoma of kidney in wall of hydronephrotic sac. ×25.

phrosis. The right kidney findings were normal. A left nephrectomy was done October 28, 1940. Upon exposing the kidney it was found to be enlarged to three times its normal size; there was a sharp kink in the ureter at the uretero-pelvic junction and a large anomalous vessel passed to the upper pole.

Pathologic examination by Dr. L. C. Knox revealed a hydronephrosis and adenoma of the kidney (Figs. 4 and 5). Microscopic examination of sections of the renal pelvis showed that the epithelium was normal in appearance. Numerous areas of extravasated blood appeared in the underlying stroma, together with patchy lymphoid infiltration. Sections of the kidney showed widespread lymphoid infiltration within the interstitial tissues. Some of the glomeruli were obliterated by fibrous ingrowth, many of the tufts were markedly congested. Beneath the renal capsule there was a small growth composed of acini lined by cu-

boidal cells. This merged imperceptibly at its edges with the tubules of the kidney.

The postoperative course of this case has been uneventful.

Case 2.—A woman, aged fifty-seven, was seen March 10, 1925. Her chief complaint was intermittent attacks of hematuria of several hours' duration which were so severe that she was left exhausted. These at-

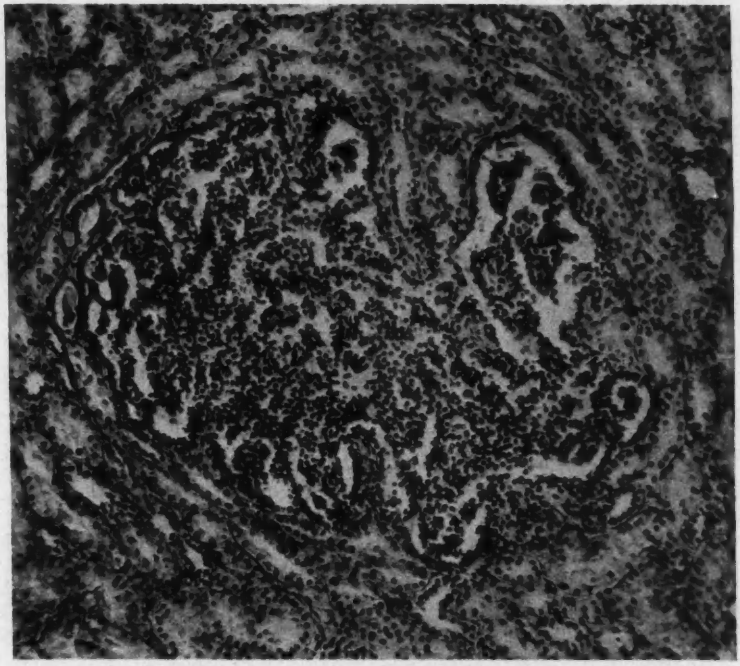

Fig. 5. Case 1. Same as Fig. 4. ×200.

tacks had extended over a period of three years. They were accompanied by pain in the right flank, chills and fever. She had had several abdominal operations and a bilateral kidney fixation. Her blood pressure was 205/110, hemoglobin 60 per cent, red blood cells 2,816,000. She was emaciated, had poor muscular tone and the right kidney was palpable, slightly enlarged and tender. Cystoscopic examination and x-rays showed the right kidney to have deficient function; the urine from this kidney contained blood and pus cells and radiographs showed the presence of two renal calculi; the left kidney findings were nega-

tive. Following a transfusion the kidney was removed. It was found to be largely destroyed being a pyonephrotic sac (Fig. 6), in the wall of the upper pole of which there was a yellowish tumor 3.5 cm. in diameter and 2.5 cm. in thickness. The histologic structure was that of an adenoma consisting of tubules lined with cuboidal cells including a large amount of fat (Figs. 7 and 8).

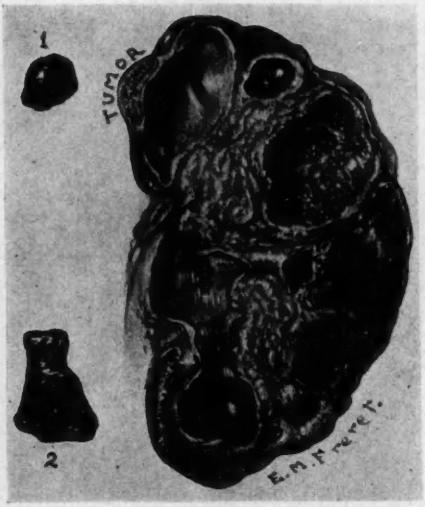

Fig. 6. Case 2. Adenoma in wall of pyonephrotic sac.

This patient made an uninterrupted recovery. Her blood pressure became reduced to 140/90 and she remained well until twelve years later, when she died of coronary occlusion.

Case 3.—A man, aged fifty-four, was admitted to St. Luke's Hospital March 18, 1938, complaining of a constant aching pain in the right costovertebral angle which had been present for three weeks. He had had occasional backache for several years. Two months before admission, he consulted an oculist whose examination revealed changes suggesting a focus of infection elsewhere in the body and on further examination he was found to have pyuria. A urologic examination was made at that time which was said to have revealed a tuberculosis of the right kidney.

Cystoscopic investigation on admission to the hospital showed a functionless right kidney (Fig. 9), a normal left kidney and a marked

congestion of the entire bladder with edema about a dilated right ureteral orifice.

The patient gave a history of a chancre in 1917, for which he had intensive treatment for two years. A spinal Wassermann test was negative in 1919 and subsequent blood Wassermanns were also negative. His father had died of tuberculosis, but the patient has no history of pulmonary disease. The physical examination gave essentially nega-

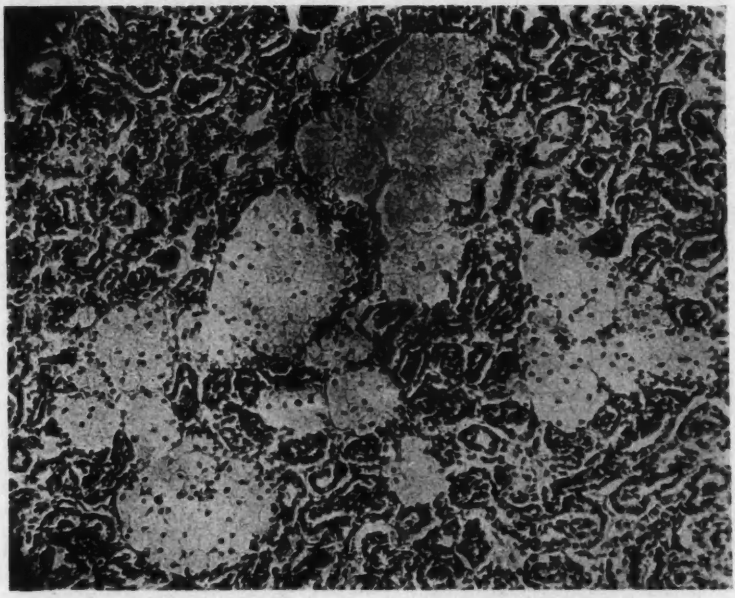

Fig. 7. Case 2. Showing histologic structure of adenoma.

tive findings. The right kidney was palpable, moderately enlarged, freely movable and slightly tender. Blood pressure was 150/106. Radiographs of the chest showed no abnormalities.

A right nephrectomy was carried out March 23, 1938, a kidney enlarged to approximately twice its normal size, containing a mass 4.5 x 3.5 x 3 cm. in size being removed (Fig. 10). The pathologic report by Dr. L. C. Knox was as follows:

Diagnosis: papillary adenoma of the right kidney with tuberculous abscess of the lower pole.

Macroscopic Examination: Specimen consisted of the right kidney. It was slightly irregular in shape, deep red in color, and measured

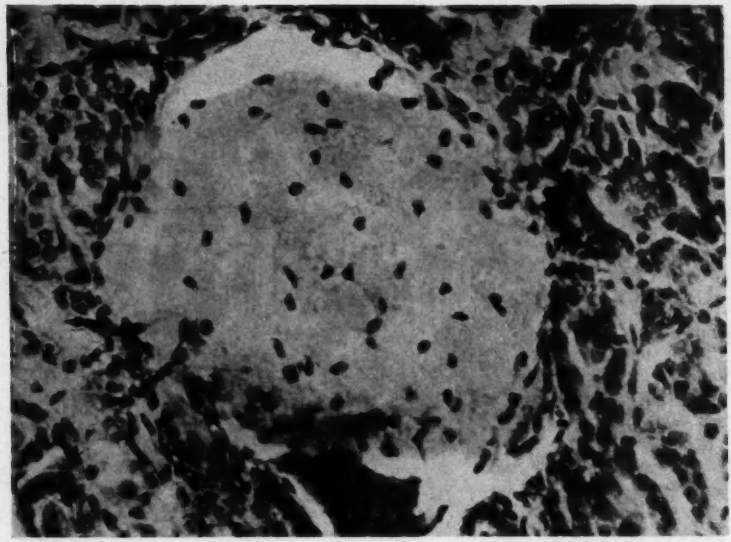

Fig. 8. Case 2. Tubules lined with cuboidal cells including a large amount of fat. ×200.

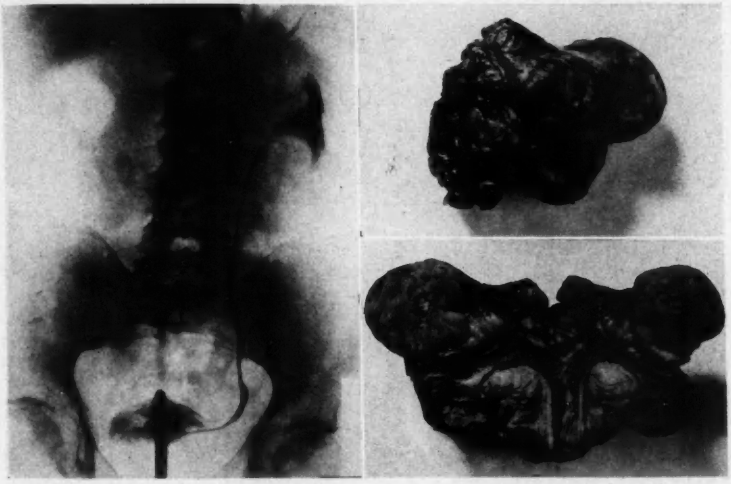

Fig. 9. *(left)* Case 3. Functionless right kidney. Normal left kidney.
Fig. 10. *(upper right)* Case 3. Adenoma in upper pole of kidney.
Fig. 11. *(lower right)* Case 3. Large adenoma of kidney. Tuberculous abscess of lower pole.

9 x 5.5 x 4 cm. It weighed 193 grams. Its surface was non-granular. Occupying the upper pole was an encapsulated, yellowish white, solid, soft tumor 5 cm. in diameter (Fig. 11). Elsewhere the calyces were markedly dilated, the medullary pyramids destroyed. At the lower pole especially was an abscess cavity 2.5 cm. in diameter, with pale, raised lining membrane. The cortex was thin and the markings poorly defined. The pelvis was widened; the mucosa, as well as that of the calyces, was slightly granular in appearance. A small bit of the ureter was included.

Microscopic Examination (Figs. 12 and 13): Sections showed a very small portion of the kidney cortex, but most of the mass consisted of a very cellular tumor having in general the appearance of a benign tumor. This tumor appeared to be derived from the kidney tubules, was composed of rather cuboidal or columnar cells, and was formed from many branching processes with very little stroma. There were a few areas of necrosis. While the cells were fairly regular, the nuclei were large and hyperchromatic and the cytoplasm was acidophilic, resembling that of the normal kidney tubules. It was possible that this tumor was still a benign one, and it was also possible that it might have invaded the blood vessels and would metastasize. The tumor showed the xanthomatous degeneration of the stroma cells which is characteristic of this group of tumors. The lining of the cavity showed granulation tissue with some atypical giant cells and poorly defined tubercles. There was not much necrosis, but the chronic infection predominated rather than the tuberculosis. There was no calcification, nor was the fibrosis typical of tuberculosis. This patient made an uninterrupted recovery and his postoperative history to date has been uneventful.

Thus we have one hydronephrotic kidney with changes in the mucous membrane showing an epithelial proliferation which probably denotes an adenoma in its earliest stages; two small adenomata associated, one with a hydronephrosis and the second with a pyonephrosis and renal calculi and a large adenoma associated with tuberculosis with advanced sclerotic changes.

It seems probable that adenomas of the kidney occur most frequently in kidneys which are the seat of vascular disease, late in life, suggesting that adenomas are the result of proliferative reaction on the part of the tubules which have been cut off from the primary blood supply as in a hydronephrotic sac, a pyonephrosis or infection, such as tuberculosis. Small adenomas will seldom give rise to symptoms but should be borne in mind as a possibility in dealing with any case of hydronephrosis or renal cyst. This might be important when contemplating plastic operations upon the renal pelvis.

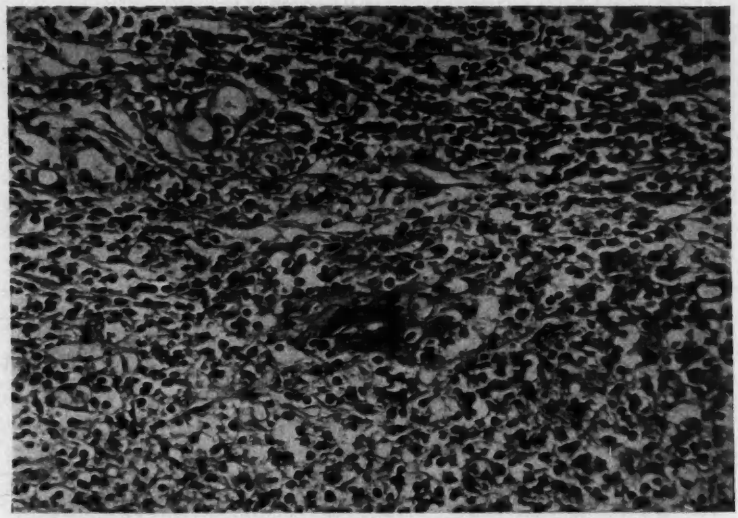

Fig. 12. Case 3. Tuberculous area in kidney site of papillary adenoma.

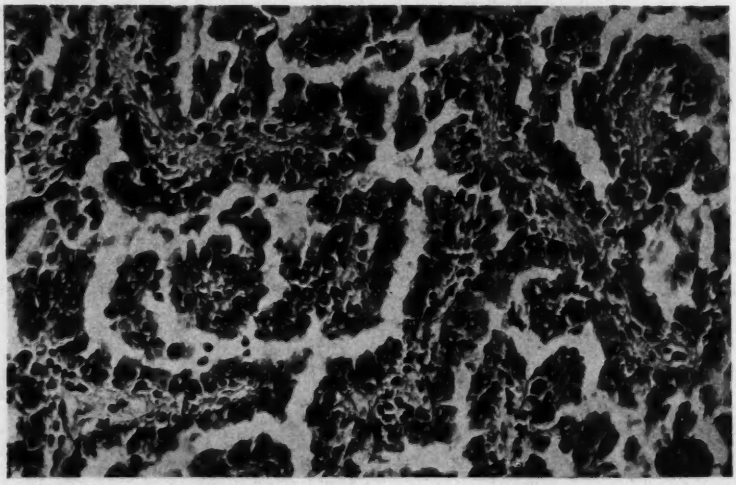

Fig. 13. Case 3. Histologic structure of papillary adenoma.

Large adenomas will seldom, if ever, be differentiated from other renal tumors before operation. While hematuria may be present, the chief symptoms will be caused by pressure upon the diaphragm, displacement of the intestines and spleen, or pressure upon the pelvic organs. The prognosis is better than one expects from the removal of frankly malignant renal tumors.

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FIBROMA OF THE TESTICLE IN CHILDREN

REPORT OF A CASE

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The recognition of benign tumors of the testicle as such is made difficult by the more frequent occurrence of benign growths in neighboring structures. On the contrary, malignant neoplasms of the testicle far outnumber the very rare malignancies found in associated tissues. Benign tumors of the scrotal contents include fibromas, myxomas, myomas, lipomas and mixtures of these, found in the spermatic cord, tunica vaginalis, epididymis, the hydatid of Morgagni and the gubernaculum. Indeed, roughly 50 per cent of growths found in these structures are benign.

Within the testis itself, benign tumors are so rare that most books on urology and pathology properly give but little space to the subject. The recognized benign tumors of the testicle include fibromas, interstitial cell tumors or hyperplasia, adenoma, cysts and various growths of teratomatous origin (such as chondromas, myxomas, myomas and dermoid cysts). Because of the case to be reported, our interest centered chiefly on those found in children and more narrowly on those of possible prenatal origin. In his Pediatric Urology, Campbell recognizes their rarity and says that benign tumors of the testis "are practically unknown in children." The reports of the past ten years were reviewed as far as they were accessible and no instance was found of a testicular tumor present at birth or noted so early in life that such a supposition was presumed.

CASE REPORT

A male infant, two weeks old, was seen in February, 1942, in consultation with Dr. A. F. Anderson. The baby was born by cesarean section on January 25, the first child of a healthy mother over forty years of age. Resuscitation was not difficult and there was no known injury to the child. The first evening, a slight enlargement and marked induration of the left testicle was noted by the nurse. Careful observation disclosed no subsequent enlargement or change in character. There was no ecchymosis. X-ray examination (soft tissue radiographs) on February 6 revealed slight increase in size of the left testicle, but no

change in density which would be diagnostic. Circumcision was done on February 4. On February 7 palpable inguinal glands were noted on both sides. Convulsive movements of legs and feet prompted a neurologic examination which was negative. The baby gained weight steadily and normally. The urine was normal on routine examination. The left testicle was found to be little larger than the right, but very hard, oval in form, not fluctuant and not adherent to the skin. The

Fig. 1. Fibroma replacing testicle, magnified about five times.

spermatic cord seemed normal. On the right side, the testicle was very soft and of normal size. It was a unique condition for all the doctors involved. A neoplasm or torsion seemed probable.

On February 8, operation was performed under drop ether. Through a small groin incision, the spermatic cord was exposed and the testicle was drawn from the scrotum. An attempt was made to enter the tunica vaginalis but it was tightly adherent to the testicle. The cord was ligated high and the testicle was removed. The skin was sutured without drainage.

The *pathologic report* by Dr. Chandler Foot is given in full. The specimen was a small reddish-brown mass approximately 1 cm. in all diameters and not at all resembling a testis. On section the surface was red and resembled blood-clot, but this material was covered with

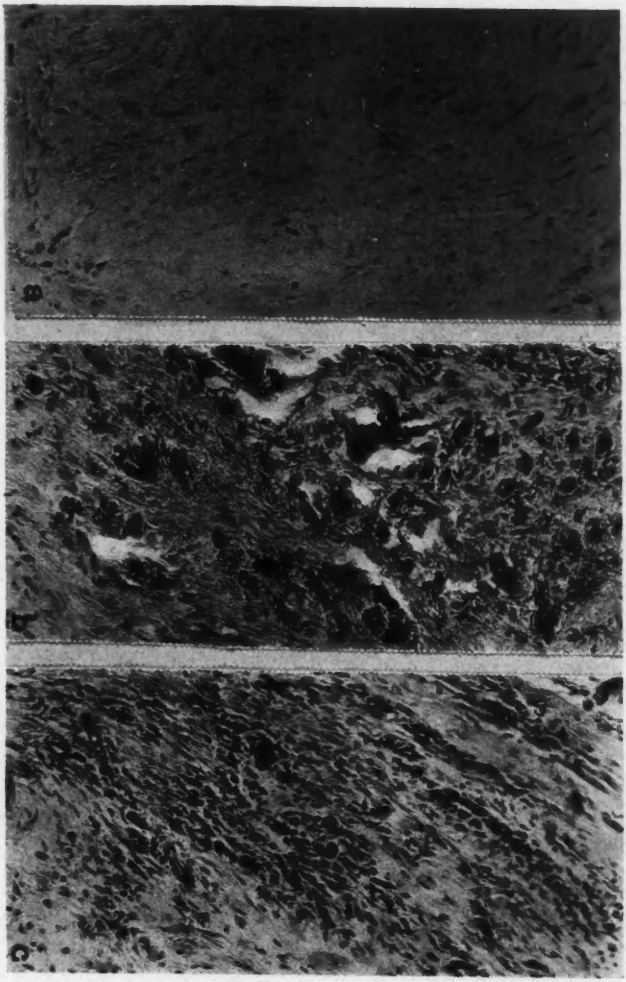

Fig. 2. Three high power views of testicular tumor showing (*a*) fibrous tissue, (*b*) many dilated vessels, (*c*) extravasated blood and pigment in cells.

a tunica vaginalis, and the appearance of the organ indicated that it had undergone torsion and strangulation. About 1.5 cm. of somewhat hyperemic vas deferens accompanied the specimen; this was not remarkable in appearance.

Microscopic Description: Section revealed a bean-shaped mass of connective tissue surrounded by thin fibers of muscle and adipose tissue. The central stroma contained several large blood vessels and numerous deposits of pigment. There was, however, no evidence of testicular structure. The site of the testis had apparently been completely replaced by this fibrous tissue. There was marked hemorrhage in the looser tissue about this central structure and scattered pigment throughout this area. In one portion of the tissue was a vas deferens in cross-section.

Pathologic Diagnosis: Probably torsion and cicatricial destruction of the testis.

Convalescence was uneventful. The baby gained weight daily and was sent home on the fifth day after operation.

In résumé, we present a report of a baby born by cesarean section, with a hard, somewhat enlarged testicle. The latter was removed two weeks later and microscopically presented a fibrous tissue mass replacing all the testicular substance, with dilated small vessels, free blood and pigment in phagocytes, a picture which suggested the possibility of prenatal torsion as the primary lesion (instead of fibroma) and fibrous tissue growth rather than atrophy as the ultimate condition.

AN INTERESTING CASE OF TESTICULAR TUMOR

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In May, 1941, a member of the Royal Norwegian Air Force, O. G., aged twenty-six, came under the care of one of us (J. C. M.) in Christie Street Military Hospital. He gave a history of having noticed a swelling in the left testicle for five years which was increasing in size more rapidly in the past two years.

The swelling was the size of a large grapefruit, solid, smooth on the surface and did not transmit light. Otherwise his physical examination revealed no abnormalities. There was no evidence of any metastases to the glands. Wassermann test was negative. Aschheim-Zondek test was weakly positive. No hormonal studies were carried out.

Operation consisted of a left orchidectomy, performed May 21, 1941.

Pathologic report by Dr. G. W. Lougheed gave the following information:

Diagnosis: Embryonal type of carcinoma of testicle (seminoblastoma).

Tissue consisted of right testicle measuring 9 cm. x 8 cm. On section it cut with a rubbery consistency sensation. The normal testicle structure was replaced by a mass of greyish, granular tissue, the center of which was necrotic.

Microscopic slide showed irregular groups of very vesicular cells, showing numerous atypical mitotic divisions. Large areas of the tissue showed a mass of degenerating vesicular cells which in some areas had a tendency to pseudo-glandular formation. There occurred irregular areas of hemorrhage throughout the growth. There were very few areas of inflammatory infiltration.

The patient was sent to the Department of Radiology of the Toronto General Hospital and came under the care of one of us (G. E. R.) and these series of treatments were carried out.

First Series (June 5-21, 1941): Left abdomen—anterior, lateral, posterior. Factors: 400 K.V.; distance, 100 cm.; m.a., 5; portal, 10 x 20 cm.; filter, 6 mm. cu., dosage, 300 r per portal per day; total, 1200 r. per portal.

Second Series (Aug. 25-Sept. 26, 1941): Factors: Same as in first series. Dosage, 300 r. per portal per day; total, 1500 r. per portal.

Third Series (Sept. 11-Oct. 1, 1941): Right lower chest and upper epigastrium—anterior, lateral, posterior. Factors: Same as in first series. portal, 20 x 20 cm. Dosage, 300 r. per portal per day; total, 1800 r per portal.

In September, 1941, a mass appeared in the epigastrium which was a secondary growth, and a further secondary growth the size of a 50 cent piece was demonstrated in the right lower chest. The patient went downhill very rapidly losing strength and weight. It appeared that he was going to die in a very short time.

It was at this time that urologists were getting very keen about orchidectomy for metastases from carcinoma of the prostate. As the metastases of this patient were from the genital tract it was decided to do an orchidectomy and see what the result would be.

He began to improve immediately and radiographs were taken of his chest at monthly intervals from November to January, 1942, showing the secondary growth to have diminished gradually. The mass in the epigastrium also underwent marked regression so as to be no longer palpable. He improved in strength and was discharged to a Norwegian Air Force Convalescent Camp in the Huntsville district. His strength returned and he won some ski competitions during the winter. He was examined by us in May, 1942, and appeared in the best of health and was returned to his unit. The Medical Officer then returned him to his full duty.†

DISCUSSION

This case is presented as one of unusual interest, and we believe illustrates the favorable effect upon cancer of the elimination of sex gland secretions. At the time of his last series of x-ray therapy in September, 1941, the patient was going downhill definitely. At this time the remaining testicle was removed, following which his condition immediately began to improve and the final result was better than could be expected reasonably from x-ray therapy alone. The opinion reached was that the removal of the remaining testicle was responsible for this increased benefit. The slides have shown the diminution of the metastases in the right lung and the mass finally regressed in the epigastrium so that it could no longer be felt by palpation. Both the secondary growth in his lung and the mass in the epigastrium have received very heavy irradiation.

Another patient who had large secondary growths in the chest from a teratoma of the testicle was greatly improved for a time by orchidectomy but finally died. The temporary improvement was very definite but he started to go downhill as if the substance causing the improvement had ceased to act.

†(August, 1942): Since the first report above was presented the original mass in the right lung has recurred and is now under x-ray treatment.

AN INTRA-ABDOMINAL OPERATION FOR CRYPTORCHIDISM

HUGH H. YOUNG, M.D.

From the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore, Maryland

E. W., aged thirty-four years, was admitted October 30, 1941. At birth the patient was pronounced by the midwife to be female and was reared as a girl. The mother lived only a few years and the child, brought up by others, led an unhappy life because when only a few years old, it realized that it was different from other children and before long, began to believe that it might be male.

The patient shaved, had no breast development, had never menstruated, had a vaginal pouch far back in the perineum into which the urethra opened. There was no palpable cervix uteri. The phallus was hypospadic and was held far back by a marked chordee. The scrotum was empty, and gonads were not palpable in either groin.

With the patient in the Trendelenburg position, through a median abdominal incision the pelvis was thoroughly explored after introduction of my four-bladed self-retaining retractor.† There were no tubes or uterus present. On each side a vas deferens was plainly visible beneath the peritoneum as it coursed upward from the posterolateral wall of the bladder on each side over the pelvic brim across the vessels, above which it joined an elongated spread-out epididymis which ended in a small testicle that projected into the abdominal cavity. The testicle was covered by peritoneum. The situation was identical on both sides. The testicle lay about 5 cm. from the middle line and was held in this position by a fatty cord about 8 mm. in diameter which ran upward toward the kidney. I decided to expose the vas deferens extraperitoneally by simply separating the peritoneum from the abdominal wall and following this into the pelvis by the side of the bladder, then upward along the lateral wall of the pelvis, following the vas deferens. This was easily accomplished. When the spread-out epididymis was reached the adhesions were more pronounced, but the peritoneum was finally elevated without injuring the isolated tubules of the epididymis. When the testicle was reached, it was necessary to make a circular incision in the peritoneum around it in order to separate it from the peritoneum which covered it. The peritoneum was then freed without difficulty from the constricting fatty cord which extended upward for a distance of 5 or 6 cm. Palpation of this cord gave no evidence of an artery. On dividing it very little bleeding occurred. By placing a clamp on this fatty cord, which was left attached to the upper part of the testicle, no difficulty was experienced in drawing the testicle down

†A motion picture in color by Mr. William P. Didusch, depicting the various surgical procedures employed in this case, was shown.

to the region of the internal inguinal ring. Running off from the epididymis and vas were two cords, one which extended downward to the internal ring. This seemed to be muscular in character and probably was gubernaculum. Running externally towards the pelvic wall was another cord which seemed to contain small blood vessels. No definite artery was palpable, but this cord was carefully preserved after being separated from adjacent tissues and followed upward along the lateral wall of the abdomen as far as possible. The gubernaculum was divided, completely liberating the cord and the vessels. The finger of the right hand was then inserted above the iliac vessels through a depression which was recognized as the internal ring. Through this the finger was easily pushed until it was visible beneath the skin covering the groin. An oblique incision was made upon the finger which was then brought out through the wound. A clamp was then inserted through the inguinal wound and internal ring and grasped the fatty cord below the testicle. Traction was made and the testicle, epididymis, vas and veins were drawn out through the inguinal wound. The cords were found to be sufficiently long to allow transplantation to the bottom of the scrotum. Another finger then was inserted into the inguinal canal and turned downward so as to pass out through the external inguinal ring which was thus greatly dilated and on down into the scrotum until the lowest part of this had been reached. Having accomplished this an incision was made upon the finger tip within the scrotum through its lateral wall. The thigh was pushed up by an orderly to a flexure of about 45 degrees, and an incision made on its inner side opposite the scrotal wound. The fascia lata was exposed. By inserting a clamp through the scrotal wound and up through the external ring, the fatty cord, which was still attached to the testicle, was then caught and drawn down through the external ring down into the depths of the scrotum and out the scrotal wound. No difficulty was experienced in approximating the fatty cord to the fascia lata with chromic catgut sutures. This held the testicle in the lowest portion of the scrotum, which was then sutured to the edges of the wound in the thigh with catgut. The wound in the groin was then closed as for hernia, using a continuous No. 2 chromic catgut suture to approximate muscle and tendon to Poupart's ligament, and a second layer bringing together the fascia and the outer portion of Poupart's ligament. This left only a tight external ring through which the cord emerged.

On the left side the technique was similar to that described above. The peritoneum was quickly separated from the abdominal and the pelvic walls, the vas, well supplied with blood, was followed out to the frayed epididymis, the peritoneum divided around the testicle, the fatty cord above it divided and ligated. The freed gonad was drawn down by a long clamp which was passed through the scrotal wound and out along the inguinal canal into the extraperitoneal space where the fatty cord attached to the testicle was grasped, and the gonad drawn down by this clamp through the internal ring and inguinal canal, down and

out through the scrotal wound where it was attached, as on the opposite side, by sutures placed through the fatty cord and fascia lata. The closure of the groin and scrotal wounds was the same as on the opposite side. Investigation then showed a hole in the peritoneum on each side through which the testicle had been disengaged. These were easily approximated by continuous plain catgut sutures, the abdominal wound closed in layers, with plain catgut for the peritoneum, chromic catgut for the muscles and fascia, plain catgut for the subcutaneous fat and continuous interrupted silk suture for the skin. A small rubber wick was placed at the lower angle of the wound for drainage. This did not extend into the peritoneum. Both thighs were held flexed at an angle of 45 degrees, and the patient was returned to the ward, where he was placed with two pillows beneath the knees to maintain this flexion. A catheter had been inserted into the urethral orifice in the perineum for continuous drainage of the bladder.

Most of the operation was done under spinal anesthesia, assisted only at the last by gas-oxygen-ether. At one time there was some evidence of shock, but this was quickly combated by intravenous fluids. The immediate convalescence was entirely satisfactory, and all wounds healed per primam.

Three weeks later a second operation was done. The scrotum was liberated from the thigh on each side by dividing the anastomosed skin and the fatty cord which ran from the testicle to the fascia lata. The scrotal wound was closed on each side with interrupted sutures of fine silver wire. The wounds in the thigh were similarly approximated.

A first-stage operation for hypospadias was then carried out. This was directed towards removing the congenital fibrous cords which held the penis back in marked chordee. The thin strip of very fibrous skin in the median line was excised. The edges of the wound on each side were elevated and the fibrous cords beneath the corpora cavernosa, which contributed greatly to the chordee, were also excised from the perineum up to the glans. In order to completely liberate the penis, it was necessary to make transverse incisions through the skin. These were made far back on each side through the scrotum and far down through the redundant hooded foreskin. These four incisions, each of which was about 6 or 8 mm. long, completely freed the penis, which could then be drawn out straight and was at least two to three times as long as it appeared before. The edges of the skin were then approximated with very fine silver wire sutures, which also picked up the fascia of the corpora in the median line. When tied this suture drew the two edges of the skin well down into the furrow between the corpora and obliterated the space, thus producing, when healed, a furrow preparatory to the next operation to make a urethra. The penis was drawn upward against the abdomen and held there by sutures which passed through the glans and through the abdominal skin and were tied with an intervening rubber band for continuous traction.

Following this operation the convalescence was satisfactory. All

wounds healed well. The penis was straight and well prepared for the second stage plastic to make a urethral tube of skin.

The second-stage operation was carried out thirty-one days later. A urethrotomy was first made far back in the perineum, and a catheter inserted into the bladder for drainage. No effort was made to excise the pseudo-vaginal pouch. The usual incisions were made parallel to the median line on each side to form a urethral tube. These extended from the glans backward through the inner side of the bifid scrotum on each side and back through the perineal tissues and around the orifice of the urinary meatus far back in the perineum, and only about 1 cm. in front of where the catheter emerged. This strip of skin was freed on each side sufficiently to allow its being drawn together to form a tube by using 0000 chromic catgut with a Dulox needle. This continuous stitch turned in the edges of the skin for a distance of about 5.5 inches. The wound was treated with 2 per cent mercurochrome. In the scrotal region a second approximation of tissues was made over the tube with 0000 chromic catgut. This did away with the bifid character of the scrotum. The skin was then approximated with a vertical mattress stitch of very fine silver wire. This approximated fairly broad surfaces of skin together from the new made meatus in the glans back to the end of the wound in the perineum, almost 6 inches in length. Examination then showed that there was tension in one place in the penile skin. This was relieved by a dorsal incision through the skin which went through the subcutaneous tissues but did not enter Buck's fascia. The wound thus produced was approximated with interrupted sutures of silver wire (Heineke-Mikulicz), leaving one end open sufficient to allow any serum to escape. The penis was again held up against the anterior wall of the abdomen by the combined use of sutures and an intervening rubber band, as after the first penile procedure.

Although the patient had been placed on sulfathiazole, a pyocyaneus infection occurred, and three small areas of suppuration developed in the six inches of newly made urethra, resulting in fistulæ which were closed several months later. The penis is straight, the rest of the very long newly made urethra is satisfactory, and the urine is voided in a good stream through the meatus just back of the glans. The testes are still small but in good position.

COMMENT

The main object in presenting this complicated case is to stress the value of the intra-abdominal operation in facilitating the freeing of the testicle and its cords and the satisfactory performance of orchidopexy. I am firmly convinced that when cryptorchidism is intraperitoneal on both sides, the operation which I have carried out through a midline abdominal incision and extraperitoneal exposure and freeing of the testicle offers manifold

advantages. I am confident that in the case which I have reported, without this technique it would have been practically impossible to have secured the satisfactory transplantation of the testes to the lower part of the scrotum. I believe that the same technique would also be satisfactory even for cryptorchid testes much lower down within the abdomen, as the intra-abdominal extraperitoneal exposure of the gonad and cords gives a far better chance to free the restricting bands without injuring the vascular supply. It also seems probable that in unilateral abdominal cryptorchidism the technique which was followed may prove of great assistance for the reasons above described in carrying out transplantation to the bottom of the scrotum. In a good many cases we have employed flexion of the thigh to avoid too great tension upon the cord, after the modified Torek operation. After two weeks the pillows are removed from beneath the knees and the thighs straightened out. The patient is out of bed at the end of the third week. Extension and flexion of the thighs are usually carried out to increase the low position of the transplanted testicle. This swinging motion of the lower extremity, with the patient in the standing position, is carried out several times daily until the time when the scrotum is detached from the thigh.

CONCLUSION

I wish to reiterate that for successful orchidopexy, it is important to hold the testicle down in the bottom of the scrotum with sutures to the thigh. I have found it preferable not to suture the testicle itself but to place the sutures either through the everted tunica vaginalis or fatty cord or gubernaculum if possible. This modification of Torek's operation prevents injury to the testicle when the scrotum is separated from the thigh. Flexion of the thighs also contributes to the success of the operation. Above all, I wish to emphasize that for testes within the abdomen a median line abdominal incision and an extraperitoneal freeing of the testis and its cords greatly facilitate testicular transplantation to the bottom of the scrotum.

ANOTHER RESECTOSCOPE

C. D. CREEVY, M.D.

From the Urological Division of the Department of Surgery, the Medical School, Minneapolis, Minnesota

Nesbit has established firmly the advantages of a resectoscope which can be operated with one hand, leaving the other free to palpate the prostate through the rectum, and to push the gland toward the cutting loop. Pressure by the index finger also serves to elevate and to make visible portions of the gland partly detached but flattened out by the pressure of the sheath.

The prostate may be pushed toward the resectoscope by the finger of an assistant or by means of the Fillis bag, but these methods do not give the operator the perception of depth which contributes so much to thoroughgoing resection.

Nesbit's instrument is beautifully conceived and executed, and does an excellent job in his hands, but I have found the action of the spring which moves the loop into the sheath a little dis-

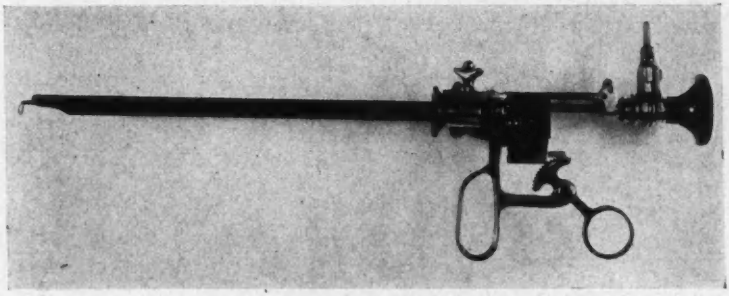

Fig. 1. Modified Nesbit resectoscope.

concerting; moreover, this movement must be aided by abduction of the operator's thumb. Abduction of the thumb is usually employed only to place the thumb in an advantageous position; hence the abductor is relatively weak and easily fatigued. To use the Nesbit instrument well, therefore, one must train and develop the abductor pollicis.

It was doubtless only laziness that prompted me to avoid this

training by having a handle similar to that of the McCarthy punch attached both to the Stern-McCarthy and to the Nesbit resectoscopes (Fig. 1). Because the elements of the handle do not cross, the loop is pulled into the sheath by adduction of the thumb. The adductor muscles are regularly used in grasping, and are ordinarily so well developed as to require no special training. Consequently, I have found the instrument easier to use than that of Nesbit. I have had no experience with the modification of the Stern-McCarthy resectoscope devised by Gibson. This achieves the same end by a different mechanism.

The technique employed is essentially that of Nesbit, which aims at preliminary partial detachment and devascularization of the lateral lobes so as to minimize bleeding during the ensuing rapid, piecemeal excision of the lateral lobes. Contamination of the forefinger by the rectum is prevented by the O'Conor sheath, and the Foley bag is employed for postoperative drainage. The objective of the operation is to approach as closely as possible to transurethral prostatectomy. Since the largest amount of tissue thus far excised at one sitting with this instrument (using a size 32 sheath) has been 155 grams, and the largest amount removed from one patient, 199 grams, transurethral prostatectomy seems feasible.

The handle of this instrument was devised and constructed for me by Mr. John Phelan of the Central Scientific Shop of the University of Minnesota, Minneapolis.

DISCUSSION

DR. CHARLES M. MCKENNA (Chicago, Ill.): Dr. Young is to be complimented on his foresight in making a motion picture of this difficult technique.

At the Research Hospital in Chicago, we have the opportunity to see a number of these cases and the average one is not at all difficult, inasmuch as the testicle is either in the canal or just below, attached to the superficial fascia. In this type, we have encountered no difficulty in following the technique as described in a previous article.

You will note in Dr. Young's title, the word "high" is emphasized. That type is less easily managed than the average case seen in routine work. From the moving picture, I imagine this testicle is opposite the umbilicus. We have had some cases which would be in this classification, but we have never attempted correction through an incision such as described by Dr. Young; however, in our next, we will employ this technique.

Last summer, we had a case of bilateral cryptorchidism. The right side had been brought down, but the left was not palpable, and there was no evidence of the position of the testicle. On operation, it was found well up opposite the umbilicus, firmly attached to the posterior peritoneum. It was necessary to make a circular incision around the testicle, so as to slide the peritoneum with the testicle attached down below the external inguinal ring. It was thus put in position at the top of the scrotum without too much difficulty. It was impossible to bring it down any further at this time because of the length of the cord. The peritoneum was closed without any attempt to repair the hernia associated with it.

The patient was twenty-three years of age and it is easily understood that it is more difficult to do this operation on one at that age than on a seven-year-old child. He returned fourteen months later and requested that we complete the operation for cosmetic effects. We found the testicle a little further down in the scrotum but not sufficiently lowered for normal position.

In this second operation, after some trouble in removing adhesions, the testicle was placed fully in the bottom of the scrotum and gave the same general appearance as its mate on the opposite

side. The hernia was also repaired. I do not advocate these two-step operations because of the difficulty always encountered in the second operation and the time involved. In this particular case it was a success, but I would caution anyone against this procedure except in unusual circumstances. The motion picture shown this morning demonstrated that a two-step operation is unnecessary and, in my opinion, that is a very important contribution.

There is one point I should like to emphasize—the preparation of the scrotum for the testicle. In all our cases of undescended testicle, we have found a stricture in the scrotum. This should be dilated and that is usually done by placing a gauze pack well into the scrotum so that when the testicle is ready for position, the stricture will be completely dilated and the testicle can be placed without any fear of atrophy or pressure.

Some cases referred to the Research Hospital have had long courses of hormone treatment. Whether it was happenstance or not, we discovered two cases with complete caseous degeneration. That may not have been due to the treatment alone, but we are inclined to be cautious about hormone treatment in patients over twelve years of age.

There is one question I should like to ask Dr. Young. I never criticize anything he does, but the last part of his picture was not shown very clearly and I could not discern the technique. When you do a Torek operation, do you bring the testicle out through the window in the scrotum and attach it to the leg?

DR. YOUNG: Generally, yes. We attach it by means of that little fibro-fatty cord. In some cases we use the gubernaculum testis and at other times we use the tunica vaginalis turned inside out. We try not to put a suture through the testicle, but leave the testicle in the scrotum, have it in close to the position, so when it is cut apart later, it won't be necessary to dissect it out or cut through.

DR. MCKENNA: That is fine. That is just what I wanted to hear. Since we developed that operation some years ago, bringing the gubernaculum through the window of the scrotum and attaching it to the fascia lata and making anastomosis, we have had no difficulty. Since that time, we have also used part of the tunica vaginalis when the gubernaculum was not sufficiently developed to make the attachment.

We are frequently asked how long the patient can go with this attachment. Well, our patients can go six weeks, six months, or six years without limiting their activities. When they do return, they remain just long enough to do the detachment and put in a few stitches in the leg and the scrotum. To date, we have had excellent results. We have also been repeatedly asked whether we use the Torek operation. We do not because we believe it results in injury to the testicle.

One more point on the hormone treatment for cryptorchidism—many authors have recommended it, but it should be prescribed with reservation and after a sufficient number of rat units have been given, it should be discontinued and the testicle brought down into the scrotum. We prefer to do the operation before puberty, between the ages of seven and nine, if possible.

In conclusion, I should like to bring your attention to the last step in Dr. Young's operation. He placed a forceps under the cord to determine the degree of relaxation. In this case it was not taut, so the patient could lie flat in bed without any danger of atrophy of the testicle. We have recommended that where the cord is inclined to be taut, it is a simple matter to place a pillow beneath the knee on that side. This can be done before the wound is closed and it relaxes the cord. This cannot be emphasized too much, for after a splendid operation, the result may be lost if there is too much tension on the cord.

We certainly appreciate Dr. Young's splendid paper. I am very happy to have had the opportunity to be here during his presentation. Thank you!

DR. GEORGE F. CAHILL: In relation to the movie shown by Dr. Young, it might be interesting to know that needle biopsies on the small undescended testes have shown some interesting results. One case so done showed on investigation that the chromosomes were of the female pattern.

DR. LEON HERMAN: May I ask Dr. Young whether he would apply this technique to cases in which the testicle is situated immediately beneath the internal ring?

DR. ALEXANDER STEVENS: May I ask Dr. Young whether he could palpate the spermatic artery, and, if so, where it came from?

[NOTE: Dr. Young requested that his closing discussion be omitted.]

DR. C. D. CREEVY (Minneapolis, Minn.): I haven't anything to add, except to say that because of his many other interests, I haven't been able to interest Mr. Wappler in the production of this instrument.

As an afterthought, I don't recommend transurethral resection in a gland as large as the one mentioned in my paper.

SECOND DAY, MAY 28, 1942

A CASE OF PSEUDOHYDRONEPHROSIS WITH UNUSUAL COMPLICATIONS

GEORGE F. HOCH, M.D.
New York City

The case I am reporting was a true hydronephrosis at operation but followed an injury at which the ureter and kidney were injured resulting in a calcified shell intimately adherent to the surrounding structures.

Johnson and Smith call attention to the misnaming of this type of cyst as a pseudohydronephrosis. Crabtree added much to our knowledge regarding this lesion when he added three cases to those abstracted by him from the literature up to 1935. His cases were seen or operated on from two to seven months following the injury. The case here reported, as well as that of Johnson and Smith, was diagnosed many years after the injury occurred.

D. D., a trained nurse aged twenty-four, was admitted May 20, 1941, and had a more or less stormy medical history. After her present operation she admitted that at the age of twelve she had been in an automobile accident at which time she was said to have had some internal injury, the nature of which was not determined. In 1937, while in training, she had an attack of grippe which readily subsided. Roentgenograms of her chest at that time showed no abnormalities. In 1938, her appendix was removed. She was admitted to the hospital for the first time in January, 1941. Ten months prior to that admission she had night sweats, cough with blood-tinged sputum, general malaise and loss of weight. Roentgenogram at that time was said to show an active pulmonary tuberculosis. Bed rest for three months at home was followed by eight months in Trudeau Sanatorium. She was pronounced cured and able to return to work.

In December, 1940, this patient again developed a productive cough but the sputum did not contain blood. The day before this admission she felt chilly and had a return of productive cough. She had marked headache with pains in the chest and legs. She stated she had had frequent bilateral frontal headaches with nausea and vomiting for several years. These occurred two or three times a month and were most marked at her menstrual period. She had no symptoms referable to her urinary tract. Examination of her eye grounds revealed nothing of im-

portance. Chest roentgenograms gave negative findings and her blood count showed a mild secondary anemia. Her temperature range was from 104 to 98 in four days when she was discharged.

Her chief complaint on the present admission was poor vision and pain in the left eye. The headaches, of which she previously complained, persisted. For a few months she had had some dizziness and felt as though she would fall but never did. There was no association at this time with her catamenia. Four days ago she had severe pain in the left eye when looking to left or right but not when looking straight ahead. The vision of the left eye was blurred and there was a loss of vision in the lower lateral field when the right eye was closed. She had a feeling as though "something was pushing her eye out."

Examination of her eyes by Dr. Henry T. Smith showed her vision to be 20/40 in the right eye and 20/200 in the left eye. The eye grounds showed the following changes: (1) left fundus 3 D. swelling of disc; (2) marked venous engorgement; (3) flat smooth hemorrhages in periphery and macular area; (4) telescopic field in left eye. Roentgenograms of teeth, sinuses, skull, orbital foramina and chest showed no abnormalities.

A diagnosis of intracranial new growth was made. Dr. Irving Pardee saw the patient in consultation and I give his findings and interpretation: "On her admission there was an acute pupilloedema in the left eye with hemorrhages and increasing blindness. The right disc was also blurred. She was somewhat confused, with a slight difficulty in getting words, though no definite aphasia. There was some unsteadiness in the gait and ataxia in the finger-to-nose and heel-to-knee test on the right side. There was slight asterognosis on the right. The reflexes were equal and exaggerated and there was no Babinski reflex. The spinal puncture done at a later time showed a marked increase in pressure with a normal serology. She was transferred to the Neurological Institute following her operation where the neurologic findings showed a slight weakness in the right upper and lower extremities with veering to the right when walking. There was dysmetria on the right side in both arms and legs. Succession movements were poor on the right. There was a slight slurring of the speech. There was a slight right hyperflexia without Babinski reflex. The examination of the eyes showed the left disc pale, irregular and engorged. There was marked defect of the visual field in the left eye. An encephalogram was done which showed a normal appearance. The spinal fluid showed a protein of 37.

"The patient was discharged from the Neurological Institute with a conclusion that there was no evidence of an expanding intracranial lesion at that time. Two weeks later the visual fields showed a loss of the lower half of both visual fields, which was almost complete in the left eye. The right eye was normal. Her subsequent course has revealed a gradual, progressive improvement following her condition in the hos-

pital. The right knee jerk is greater than the left and the right grip is weaker. The visual field is still defective in the lower half. There are no sensory changes."

Dr. Pardee's conclusion was that the patient showed evidences of a left frontal focus in the nature of an inflammatory expanding lesion which subsided. There was every evidence at one time to suspect a brain abscess which did not eventuate.

The medical consultant in addition found a fixed mass in the right upper quadrant, extending from the costal margin about 3 inches below this level. Intravenous urograms showed good function and normal filling on the left side. On the right there was no evidence of function and the tumor mass partly outlined by calcium deposit was noted. Cystoscopic examination, May 26, 1941, showed a normal bladder. Catheter on the right extended to the kidney region. Pyelographic medium was obstructed at the ureteropelvic junction. Blood count showed 4,800,000 red blood cells with 97 per cent hemoglobin; 8,700 white blood cells with 70 per cent polynuclears. Urine analysis was negative as was a Wassermann reaction. Blood urea nitrogen was 10.6 and blood sugar 87. Sedimentation rate was 4 mm. per hour.

A diagnosis of tuberculosis of the right kidney was made and it was presumed the brain lesion was probably a tuberculoma. At operation May 28, a right subcostal incision was made under cyclopropane anesthesia. Under the muscles but adherent to the transversalis fascia was the kidney mass. There was no perirenal fat nor was Gerota's fascia noted. The removal of the mass was tedious and was entirely done by sharp dissection. Before going far the thin-walled sac was opened and about a pint of clear straw-colored fluid escaped. Only a small piece of tissue was left in the upper portion of the wound. The peritoneum was opened in three places because of the adherance of the sac. Because of these accidents 4 gm. of sulfanilamide was put in the wound after closure. The ureter and renal pedicle were not found and there was no bleeding. A small Penrose drain was inserted just below the muscles and the wound closed in the usual manner. Other than a cyanosis of four days due to the sulfanilamide postoperative convalescence was uneventful and the patient was transferred to the Neurological Institute on her sixteenth postoperative day. Smears of the fluid showed no organisms and the culture was sterile.

Pathologic Report: Chronic hydronephrosis with atrophy of right kidney.

Macroscopic Examination: The specimen consisted of the right kidney. The tissue presented no structure which resembled a kidney. It appeared to be the wall of a cystic tumor, the inner lining of which was covered with a scale-like layer of calcified material. Externally at one point, there was some striated muscle present and at another point there was a structure which bore some resemblance to a renal pelvis

with collapsed calyces. The calyces, however, were blind. There were no renal vessels recognizable as such and no ureter could be found.

Microscopic Examination: Sections showed a small amount of renal tissue very much atrophied, tubules dilated or shrunken and the epithelial cells very minute. Scarcely any kidney tissue remained which was not extensively scarred. The cystic cavity appeared to be a dilated pelvic wall composed of hyaline fibrous tissue with extensive calcification. There was no cellular tissue in the mass and no evidence of tuberculosis or active infection.

Other than a defect in the visual field the patient was improved, was well and working. I did not feel that incision and drainage would be adequate, as suggested by Colston, if our argument that the brain lesion was secondary to the kidney were true. It seemed imperative that the sac be removed as far as possible. But with a negative tuberculosis, infection or tumor, one can only presuppose it may have been secondary to some arterial changes caused by this damaged kidney.

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RANDOM THOUGHTS ON POLYCYSTIC DISEASE OF THE KIDNEYS

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I have long been impressed with the thought that the literature on polycystic disease of the kidney, as compared with the literature on most other urologic problems is relatively sparse. I can remember only two papers on the subject presented before this Association since I have been a member. One was an excellent paper read by Norris and Herman[2] at the 1938 meeting in Atlantic City. Their paper presented an elaborate discussion of the embryologic factors involved and an exhaustive review of the literature. The subject is treated rather cursorily in most textbooks; the various theories of possible etiologic factors are discussed at some length, while the clinical factors, including symptomatology, prognosis and treatment are dismissed in a few lines. All of this may well be accounted for in part, at least, by the following facts: It is not a common disease. Many patients with polycystic disease are seen and treated by the internist and never come to the attention of the urologist. For this reason many urologists, even those who are working in large clinics, see very few patients with polycystic kidney disease and the majority of these few appear to present little of urologic interest. They are, therefore, turned over to the internist, given a poor prognosis with few, if any, recommendations for treatment other than the usual hygienic measures.

A recent study of a small group of cases seen at the Brooklyn Hospital has led me to believe that the prognosis as to longevity is perhaps a bit better than is commonly supposed; that a fair proportion present symptoms of interest to the urologist, and that a few of these patients may be subjected to surgery with a reasonable expectation of improvement and prolongation of life. It has further appeared to me that there are two fairly distinct types of this disease. One of these types is noted in newborn infants, while the other, the type most commonly discussed, is noted in middle or late adult life. It is rather a striking fact that while occasional cases are reported in the newborn and a number

of others in the fifth and sixth decades, practically no cases are noted in the teens and few in early adult life. While, of course, it is quite possible that these two groups may represent different degrees of the same condition, the gross appearances and the his-

Fig. 1. Baby X. Kidneys *in situ* practically filling the abdomen.

tologic pictures, plus the age incidence, suggest that they may well have different embryologic backgrounds.

This paper is based on a study of sixteen cases seen over a fifteen-year period plus one case seen previously and included because of its particular interest. Of these seventeen cases, eight were recognized clinically but did not come to autopsy; nine were found at autopsy and in some of these the diagnosis had been assumed but had not been definitely determined. Over this fifteen-

year period 1,593 autopsies were performed. The nine cases of polycystic disease recognized at necropsy represent an incidence of 0.56 per cent or 5.63 cases per 1,000 autopsies. This is greater than the incidence reported by Braasch[1] which was one to 1,019.

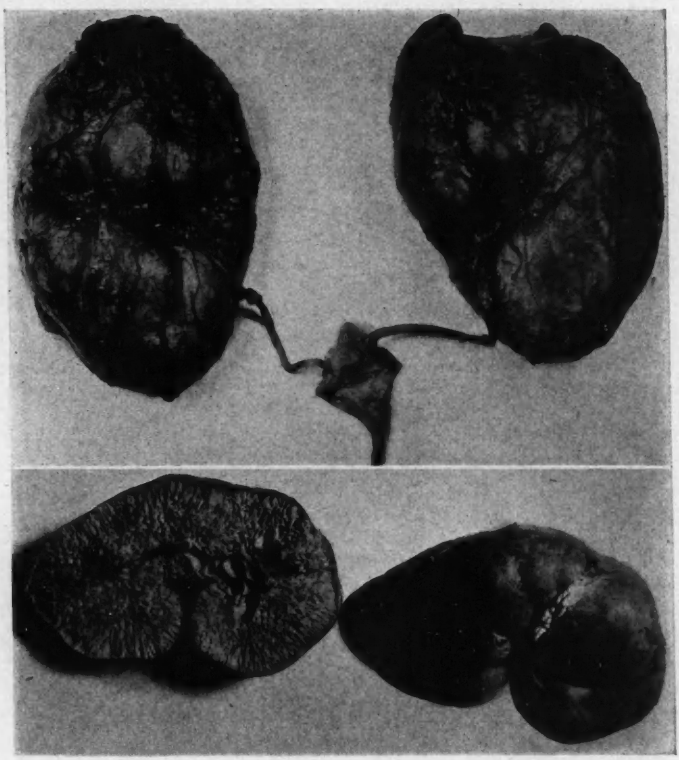

Fig. 2. *(above)* Baby X. Kidneys, ureter and bladder.
Fig. 3. *(below)* Baby X. Bisection of kidney. Although the cortex does not appear cystic, section shows innumerable tiny cysts.

The necropsies were performed on two stillborn infants, four infants in the neonatal period, and three adults. The age incidence of the entire series was as follows: seven were infants, either stillborn or in the neonatal period. The youngest adult was twenty.

Another patient was thirty-eight. The remaining eight were in their fourth, fifth and sixth decades, the oldest being sixty-nine. The average age in the adult group was 51.7.

In five of the nine autopsied cases other congenital anomalies

Fig. 4. Baby X. This slide is typical. The kidney is composed almost entirely of fibrous tissue and hardly any normal kidney elements.

were noted. They include: congenital cystic liver; absence of left kidney and left testicle; congenital deformity of anal orifice; club-foot and occipital meningocele; absence of anus, atresia of rectum, absence of gall bladder, hydro-ureter, bilateral club-foot and mongoloid appearance. In fourteen of the cases polycystic kidneys were proven to be bilateral. In one case (stillbirth) there

was an entire absence of the remaining kidney, while in another case (adult) polycystic disease was suspected but not proven in the contralateral kidney. In still one other case polycystic kidney was noted in one-half of a horseshoe kidney, the other half

Fig. 5. Baby X. While a number of glomeruli are seen in this field, none of them even approaches the normal structure.

being perfectly normal. Two pairs of sisters were noted among the infants, one pair occurring in consecutive pregnancies.

With one exception the pathologic picture in the autopsy specimens for the newborns was typical. The kidney or kidneys were enormously enlarged almost filling the entire abdomen and in two cases the abdominal enlargement added materially to the difficulty of delivery (Figs. 1, 2 and 3). On microscopic examination the

kidneys were found to consist almost entirely of interstitial fibrous tissue with only an occasional tubule and glomerulus and all of those were grossly deformed. This is shown in Figures 4, 5 and 6. The one exception was the case of Baby L. shown in Fig-

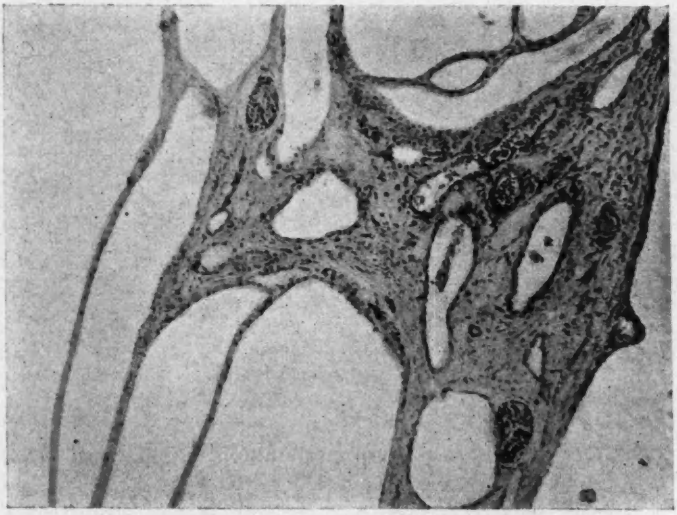

Fig. 6. Baby X. Another field showing a rather typical picture of an occasional atrophic glomeruli among cysts of varying sizes.

ure 7. The kidneys grossly and microscopically resembled those seen in adults, which might perhaps be defined as the adult type. Sections of various parts of these kidneys showed groups of small cysts and areas containing a fair number of glomeruli, some of which were fairly normal in type, as seen in Figure 8. The marked difference in the two types of polycystic kidneys, both in gross and microscopic appearance suggests, as I have noted above, a possible variation in the embryologic background.

Of the ten adults studied clinically, four were constantly hypertensive, three were intermittently hypertensive and one had normal blood pressure. Two were definitely hypotensive. It is generally understood that hypertension is part and parcel of this disease. While, of course, such a small series proves little or nothing, it suggests that hypertension is not necessarily a constant symptom.

In two of the adults studied clinically polycystic disease was not recognized until autopsy. One of these died as a result of bronchopneumonia with terminal convulsions. The other died of carcinoma of the stomach. Three years previously he had had a two-stage suprapubic prostatectomy, at which time polycystic disease was not recognized. (He made a good recovery from the prostatic operation.) It is interesting to note that of the remaining eight adults in whom the diagnosis of polycystic kidney disease was recognized clinically, hematuria was a prominent symptom in five (62.5 per cent).

Of the eight patients recognized clinically in the adult group, five were subjected to Rovsing operations. One nephrectomy was performed by one of the junior members of my staff, and was more or less of a misadventure. The patient, an infant two and one-half days old with huge polycystic kidneys, was oliguric but apparently making a bid for life. As more or less of a desperate gesture a Rovsing operation was decided upon. The kidney was delivered and incised in several places with little, if any, diminution in size. It was found impossible to replace the kidney and close the wound, so the kidney was removed. The child died six hours later. One of the Rovsing operations was performed on a thirty-eight-year-old adult who was profoundly uremic. Following the operation, which was done as a last resort, there was a slight temporary improvement. However, the condition eventually progressed and the patient died in coma twenty-seven days later. Another Rovsing operation was performed on a woman forty-six years of age because of a moderate degree of renal insufficiency and pressure symptoms. The patient made a good recovery and is in fairly good health six years later. Still another Rovsing operation was performed on a patient with horseshoe kidney, one-half of which was polycystic and the other half perfectly normal. The indication for operation was a large mass identified with the kidney. A tentative diagnosis made pre-operatively was kidney tumor. At operation a large polycystic kidney was found. Cysts were collapsed. The patient was seen eight years later and was in excellent health. Two Rovsing operations were performed for excessive bleeding. In both instances results were eminently satisfactory. One was on a man of sixty-four years in whom it was suspected, but not proven, that there was poly-

cystic disease of the contralateral kidney. The patient made a good recovery, had no further bleeding or any other symptoms referable to the urinary tract and died sixteen years later of apoplexy. This was the one case that preceded the fifteen-year period. The other case, a woman of fifty-seven known to have bilateral polycystic disease, had excessive bleeding from one side. She, too, made a good recovery and was known to be in fairly

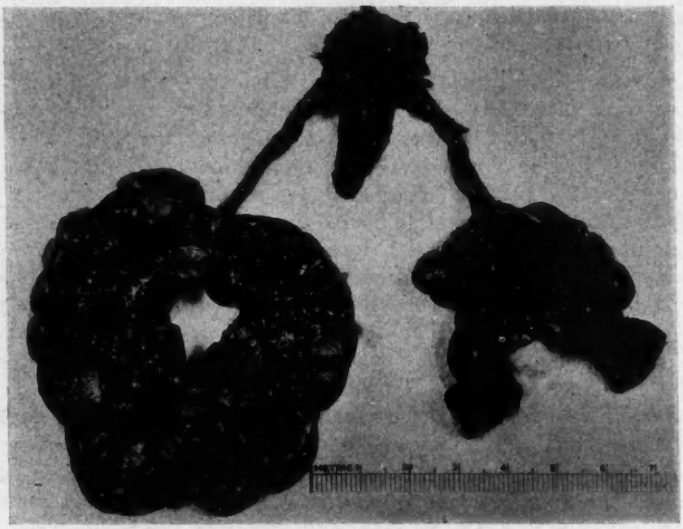

Fig. 7. Baby L. Gross specimen of kidneys, ureters and bladder. The kidneys present more nearly the picture seen in adult cases.

good health eleven years later. While these cases prove nothing, they do, I think, encourage one to consider surgery in certain selected cases. A somewhat detailed report of three of these cases is appended.

In three of the eight clinical cases, there were no urologic operations. One adult is alive and in fair health seven years after the diagnosis of bilateral polycystic disease was made. Another adult lived for one year and died from renal insufficiency. In a third adult the polycystic kidneys were recognized during an exploratory laparotomy. At the time no operative treatment

was carried out because the patient's condition was considered critical. The patient died three months following laparotomy.

REPORT OF CASES

Case 1.—A. T., thirty-one years old, white, female, was first seen at the Brooklyn Hospital Dispensary on November 10, 1927, with the chief complaints of bearing down pains when passing urine and back

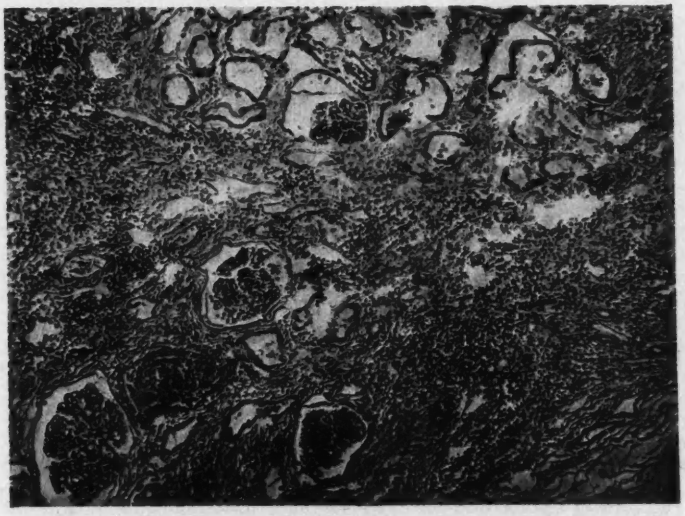

Fig. 8. Baby L. This field presents a number of tubules and glomeruli, some of the glomeruli being almost normal in appearance. This closely resembles the picture noted in the adult type.

pain. The patient gave a history of having had "kidney disease" for a ten-year period since the birth of a child. Physical examination was essentially normal with the exception of a hard immovable mass, the size of a peach, which could be palpated at the lower pole of the left kidney. The lower pole of the right kidney was also palpable. Blood pressure was 150/88. Urinalysis revealed a trace of albumin, a few epithelial cells and occasional small clumps of pus and pus cells. On cystoscopic examination the bladder was normal as were the ureteral orifices. Phenolsulphonephthalein, injected intramuscularly, was excreted in fair concentration from the right kidney within nineteen minutes and from the left within twelve minutes. Pyelograms showed both kidneys to be large, the right larger than the left. The right renal pel-

vis was markedly deformed and the ureter redundant, kinked and dilated. There was narrowing of the lumen close to the bladder orifice. Blood chemistry showed urea 32.4 mgm., creatinin 1.20 mgm. and sugar 90.9 (the patient was on a meatless diet). A diagnosis of polycystic kidney disease was made, based largely upon the pyelographic studies.

The patient had repeated cystoscopic examinations and roentgenograms and was followed in the dispensary until 1936. On April 7, 1936, she was admitted to the hospital for an elective Rovsing operation. At that time the patient had no complaints other than occasional back pains. There was no history of frequency, urgency or hematuria. On physical examination, the patient, a well-developed and well-nourished thirty-eight-year-old female, did not appear acutely or chronically ill. The heart and lungs were normal. The abdomen was soft and no spasms or rigidity were noted. The right kidney was enlarged, palpable and not tender. The left kidney could also be palpated. Blood urea was 19.56 mgm., creatinin 3.222 mgm. and sugar 111.1 mgm. per 100 c.c.

Cystoscopic examination was repeated and No. 4 catheters were passed to each renal pelvis. Urine was seen to drip rapidly from each pelvis. Phenolsulphonephthalein appeared in poor concentration from the right ureter in eleven minutes and in poor concentration from the left in six minutes. The bladder specimen showed a few free leukocytes, and a few large and small clumps of pus. The urea was 5.67 gm. Urine from the right ureter showed free leukocytes and occasional clumps of pus. The urea was 5.54 gm. The specimen from the left ureter was normal with a urea of 6.68 gm. Pyelograms showed both kidneys to be enlarged, the right larger than the left. Injection of 9 c.c. of skiodan into the right ureter did not fill the pelvis and was seen only in the upper portion which appeared deformed. The left pyelogram showed a markedly stretched-out, pressure-deformed pelvis.

On April 14, 1936, a Rovsing operation was performed on the right kidney. The kidney was delivered through a loin incision. It was found to be at least six times normal size and felt like a large bunch of grapes. It was easily mobilized, the capsule was removed and innumerable small cysts and a few fairly large cysts were incised and collapsed. The postoperative course was uneventful and the patient made a normal recovery.

The patient has been followed to date in the clinic. With the exception of moderate hypertension and some slight evidence of renal insufficiency, she is in fair physical condition six years following operation.

Case 2.—B. E., fifty-two years old, white, female, was admitted to the Brooklyn Hospital on November 27, 1923, for cystoscopic examination. The patient gave a three weeks' history of painless hematuria but did not complain of any symptoms referable to the bladder. Three years previous metrorrhagia had been treated by radium. Otherwise the patient had always been well. Physical examination at the time of admission did not reveal any positive findings. Urinalysis was essen-

tially negative. On cystoscopic examination the bladder and ureteral orifices appeared normal. No. 5 catheters passed easily to each renal pelvis. Phenolsulphonephthalein injected intramuscularly was recovered within six minutes from the left and from the right sides. Unfortunately, the report of the examination of the separate specimens was lost. They were, however, clear and the source of the bleeding was not determined at this time. The patient was discharged from the hospital on November 29, 1923.

On April 7, 1926, the patient was re-admitted. The chief complaint was a sensation of fullness on the left side along the costal margin, extending to the back. The sensation of fullness was not continuous and there was no accompanying pain. There was some nocturia (two to three times). The patient also complained of palpitations which occurred at intervals. Physical examination at this time revealed the patient to be rather obese, showing no evidence of acute or chronic illness. The heart was not enlarged and no murmurs were noted. The sounds were of good quality but faint. Blood pressure and pulse were 180/110 and 72, respectively. Electrocardiograms taken five days after admission showed premature ventricular contractions and a left ventricular preponderance. Urinalysis revealed cloudy, acid urine with a specific gravity of 1.012, urea 14.67 gm., a faint trace of albumen, 1.22 gm. glucose and an excess of indican. On microscopic study, many leukocytes were found, a moderate number of epithelial cells and a few clumps of pus. The blood urea was 47.1 mgm., creatinine 1.83 mgm. and sugar 238 mgm. per 100 c.c.

On cystoscopic examination, the bladder and ureteral orifices appeared normal. No. 5 catheters passed easily to both renal pelves. The bladder specimen showed a few epithelial cells, 13.24 gm. urea, occasional red blood cells and mucus. The specimen from the right ureter showed many red blood cells and from the left a moderate number of red blood cells. For some reason the flow of urine from each catheter stopped after the phenolsulphonephthalein had been injected so that a differential function test could not be done at this time. Cystoscopy was therefore repeated five days later. Phenolsulphonephthalein injected by the intramuscular route appeared from the right side within ten and one-half minutes in good concentration and from the left in eleven minutes in poor concentration. Retrograde pyelograms showed both kidneys enlarged, particularly the left. The right renal pelvis extended a little upward and downward. The calyces appeared somewhat spread out and the middle calyces were pushed out medially. The left ureter appeared normal but the renal pelvis was definitely deformed. The middle calyces were flattened and the minor calyces dilated in a flower-like fashion. The findings were suggestive of double kidney tumor or polycystic kidneys.

Examination of the heart was repeated. The blood pressure was 160/105. Heart sounds were of good quality but faint. The patient was deemed a good operative risk.

On April 16, a Rovsing operation was performed on the left kidney. The kidney was found to be twice the normal size and appeared to consist almost entirely of cysts varying from pinhead to lemon in size. During the postoperative course, there was a marked weight loss. The blood pressure dropped to 86/64. Heart sounds were distant, but no murmurs were ascertained and no enlargement of the heart was noted. Electrocardiographic tracings taken on May 5, 1926, showed partial heart block and prolonged conduction time. Urinalysis on May 8 revealed many pus cells, the urine being otherwise normal. Blood urea was 28.4 mgm., creatinine 3.37 mgm. and sugar 200 mgm. per 100 c.c. Hemoglobin was 65 per cent. The general condition gradually improved and the patient was discharged on May 28, 1926.

On July 13, 1926, one and one-half months following discharge from the hospital, the patient was re-admitted with a three-day history of continuous, painless hematuria, accompanied by a dragging sensation in the pelvis. On physical examination the pertinent findings were limited to the abdomen. No rigidity was noted. A tumor-like mass was felt in the region of the left kidney. On palpation of the mass slight tenderness was elicited. Cystoscopic examination revealed the mucous membrane of the bladder to be normal except for a papilloma about 3 cm. in diameter, near the right ureteral orifice. This was delicate in structure with a very fine pedicle. The pedicle of the tumor was fulgurated and the patient was discharged the following day.

In October, 1926, the patient was re-admitted for a general check-up and there was no further history of hematuria. Chest examination showed the lungs to be clear. Heart sounds were good but distant. Pulse was 72 and blood pressure 180/110. Cystoscopically there was no evidence of any growth. The bladder appeared normal. Phenolsulphonephthalein, injected by the intramuscular route, appeared within eight minutes from the right and twelve minutes from the left ureter. The bladder specimen and the specimens from the right and left ureters were essentially normal. The blood urea was 33.5 mgm., creatinine 2.84 mgm. and sugar 143 mgm. per 100 c.c.

About one year later, in November, 1927, the patient was seen again. There had been no recurrence of the bleeding and there were no other symptoms or complaints. Blood urea was 49.0 mgm., creatinin 2.5 mgm. and sugar 121 mgm. Blood pressure was 130/80.

In November, 1928, the patient was hospitalized for a cystoscopic examination. The bladder and ureteral orifices were normal. Phenolsulphonephthalein injected intramuscularly appeared from the right ureter in seven minutes in fair concentration and from the left in nine minutes, also in fair concentration. The bladder specimen was normal. The urea was 6.30 gm. The specimens from the right and left ureters were normal, the urea being 7.56 and 7.06 respectively. The left pyelogram appeared much like the one made pre-operatively. Blood chemistry was urea 28.1 mgm., creatinin 2.50 mgm. and sugar 129.4 mgm. per 100 c.c. Blood pressure was 150/110.

The patient had had no hematuria since 1926 (at which time the bladder tumor was fulgurated) until three days prior to admission on May 7, 1937, when blood was noted in the urine for two or three days. The patient had been in good health for the ten years since the previous admission with the exception of generalized malaise for the last two years. There was no history of dysuria, incontinence, nausea, vomiting or fever. Occasionally there was slight pain in the left costovertebral angle. On physical examination the patient appeared markedly older than when last seen and older than the given age (sixty-five). Temperature was normal and blood pressure 180/90. The skin was pale and dry and the lips slightly cyanotic. The abdomen was flabby and there was a tendency to gas in the left upper quadrant. The heart sounds were distant but the heart did not seem to be enlarged.

An electrocardiogram indicated partial heart block with prolonged conduction time and left axis deviation. Blood chemistry revealed the urea to be 50.39 mgm., creatinin 3.108 mgm. and sugar 117.6 mgm. The mucous membrane of the bladder appeared on cystoscopic examination to be mildly congested but no growths were noted after careful search. From the right ureter, clear urine was obtained, while from the left it was first bloody, perhaps due to trauma, but later clear. Phenolsulphonephthalein, injected intravenously, appeared from the right and left ureters within three and one-half minutes, but it was in poor concentration from both sides in seven minutes. A left pyelogram showed a dilated, deformed renal pelvis with flattened and distorted calyces. The right pyelogram also indicated flattened and deformed calyces.

Because the renal function tests showed nitrogen retention and delayed phenolsulphonephthalein excretion, it was suggested that the patient be placed on a regimen of restricted physical effort, on a high carbohydrate, adequate protein diet and a fairly high fluid intake. The hematuria having been controlled, the patient was dismissed on May 12, 1937, eleven years after the Rovsing operation on the left kidney. We have been unable to trace the patient since that time. It is interesting to note the improvement in renal function over a period of several years with a moderate relapse after ten years.

Case 3.—G. S., fifty-nine years old, white, male, called at the office in September, 1924, for cystoscopic examination. For a period of four months, the patient had had intermittent, painless, gross hematuria and loss of weight. Family and past history were non-contributory. On physical examination the patient, a rather thin, undernourished man, did not appear to be acutely ill. Positive findings were limited to the heart and abdomen. The heart was not enlarged, the rhythm regular, but a systolic murmur was noted in the aortic area and to a lesser degree at the apex. In the right lumbar region a soft, fluctuating, circumscribed mass, the size of an orange was palpated. This was not painful and was non-tender. The abdominal muscles on the right side were held firmly, whereas there was no rigidity on the left side. The patient voided 6 ounces of grossly bloody urine. An observation

cystoscope was passed into the bladder and numerous clots were washed out. Very bloody urine was seen coming in spurts from the right ureter and clear urine from the left. Feeling that the source of the bleeding had definitely been located, the remainder of the bladder was not carefully examined. Blood urea, creatinine and sugar were within normal limits. The patient was referred to the hospital for further studies with a provisional diagnosis of right renal tumor.

On September 27, 1924, another cystoscopic examination was made. A No. 5 catheter passed easily to each renal pelvis. On the left side the flow was free but on the right very slow. Both specimens were blood-tinged. On the left phenolsulphonephthalein injected intramuscularly was returned within seven and one-half minutes in good concentration. However, on the right side none appeared within twenty minutes. Injection of 6 c.c. of a 10 per cent solution of sodium iodide into the left ureter did not adequately fill the renal pelvis or ureter, the pelvis appearing markedly contracted. A right pyelogram revealed a defect obliterating the middle and part of the lower calyces. Both kidneys appeared enlarged.

With a tentative diagnosis of tumor of the right kidney, an operation was performed on October 3, 1924. Through a 7-inch Mayo incision the kidney was exposed and found to have several large cysts in the cortex. A Rovsing operation was done and recovery was uneventful. The wound healed firmly and the patient was discharged on October 22, 1924.

On follow-up examination at the office shortly after discharge from the hospital, the patient's general condition was satisfactory but hematuria had recurred and the patient again voided grossly bloody urine. Cystoscopic examination at this time showed clear urine after the bladder was washed clear of clots. The urine from each ureter was also clear. Obviously there was some further source of bleeding and a more careful investigation of the bladder revealed a large infiltrating tumor at the anterior wall extending up toward the vertex. Naturally, I was very much humiliated to have missed this obvious gross pathologic condition at the previous examination, but I was lulled into a sense of security by having located the source of bleeding which might have well accounted for all of the other symptoms. The patient was again referred to the hospital for operation which was performed on December 19, 1924. The bladder was exposed and partially mobilized. On the anterior wall a solid tumor was found. The tumor, together with a portion of the wall, wide of the growth, was excised. On histologic study the tumor was found to be an infiltrating carcinoma of the bladder, Grade III, checked by the Bladder Cancer Registry. Recovery was uneventful. At the time of discharge on February 2, 1925, the wound was firmly healed and the patient was voiding normally.

The patient lived out of town but reported by mail twice yearly throughout the remainder of his life. He stated with each communication that his health was excellent and that at no time had he had any

symptoms referable to the urinary tract. The patient died in Florida following an attack of apoplexy in October, 1940, sixteen years following operation.

This case is of particular interest since the patient not only had no recurrence of bleeding from a polycystic kidney for a period of sixteen years, but also had no evidence of recurrence of a highly malignant tumor of the bladder which had been resected at about the same time. Unfortunately, permission for autopsy was not obtained.

SUMMARY

It is suggested that there may be two types of polycystic disease with perhaps different embryologic backgrounds.

All cases of polycystic disease are not hypertensive,

Operation should be considered in certain selected cases, particularly in those cases in which bleeding is a prominent symptom.

Operation, when performed, should be done early and not as a last resort.

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THE UPPER URINARY TRACT IN CASES OF NEUROGENIC BLADDER

PRELIMINARY COMMUNICATION

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In the many studies of cord bladder no reference is made to the upper part of the urinary tract. We have searched the literature as to investigations of the kidneys and ureters in neurogenic bladder in association with brain and spinal lesions. It was a revelation to us that, with one or two exceptions, no attempt was made to study the anatomy of the kidney and ureter in these cases. Current text books either do not refer to this at all, or speak about back-pressure. Whatever knowledge we have about this subject is based largely on speculation and conjecture. With a view to clarifying some of our concepts on this topic, a series of investigations were undertaken on clinical material made available to us by the large syphilis clinic in our hospital, and by the Montreal Neurological Institute. In addition a re-study of the innervation of the ureter was attempted by means of microscopic dissections of histologic tissue in man and animals.

It appears to be the consensus of opinion among urologists that hydronephrosis and hydro-ureter are features of the neurogenic and cord bladder. Explanations given are that it is an overdistended atonic bladder generating increasing intravesical pressure, which is transmitted along the ureter and pelvis, with or without the presence of infection, resulting in dilatation of the structures; or, it is an expression of disturbance of innervation, intrinsic or extrinsic.

In reviewing the literature, the work by Plaggemeyer in 1921 is very significant. He discussed a series of twenty cases of cord bladder in which the cord had been transected at various levels, and in inflammatory lesions of the cord involving single and multiple tracts. His patients were all submitted to cystoscopy and cystography. He concluded that there was no dilatation of ureter or pelvis, and no evidence of reflux. All the cases showed evidence of impaired renal function as determined by blood chem-

istry. This inconsistency was hard to explain in the absence of structural alterations in the ureter and pelvis. Cumming, a collaborator of Plaggemeyer, investigated a series of cord lesions as to upper urinary tract pathologic lesions by means of cystoscopy, intravenous pyelography, and serial ureterograms. The data he presented were (a) ureteral orifices in cord bladders show definite mutations as observed over a period of time; (b) ureteral atony, segmental or complete, has been observed in cases of myelitis; (c) where hydronephrosis exists in paralytic bladders, infection and back-pressure are more likely to be the causative factors. In conclusion, he says that hydronephrosis is not a common sequence to paralysis of the bladder, nor is ureteral atony a common finding, except in the presence of gross infection.

Experimentally, ureteral atony, hydronephrosis and hydroureter are reported to have been produced by three different approaches. First, the mechanical approach was made by Watson Beach; secondly, Andler states he succeeded by denervating the renal artery and vein, contending that the motor fibres initiating peristalsis pass through the renal pedicle; and finally, P. Blatt quoted by Walther, achieved the same result by sympathetectomy of the kidney and ureter.

An important experimental contribution to the subject was made by Watson Beach in a number of experiments on dogs. He produced hydronephrosis by removing a small segment of the ureter and inserting a cannula into the cut ends. This resulted in atony of the ureter with dilatation above and below the cannula. The peristaltic wave, which is carried by the intrinsic nerves and ganglions, is interfered with and urinary propulsion does not occur, resulting in stasis. Beach states that, clinically, any neuromuscular disturbance of the ureter, such as injury, ends in dilatation of the ureter and pelvis.

Under the term "adynamic hydronephrosis" dilatation of the pelvis is ascribed to sympathetic-parasympathetic imbalance. Braasch states that there is a group of cases in which there is dilatation of the ureter and pelvis with no apparent ureteral obstruction. Harris and Harris have noted a hypertonic condition of the musculature which produces contractions at the ureteropelvic junction, so violent as to cause protrusion into the lumen causing a true ball valve action. The mechanism at work is an increase in

the intrapelvic pressure, and later atonic relaxation and dilatation of the pelvis. Mathé and von Lichtenberg have observed similar lesions and attribute them to some pathologic lesion of the sympathetic splanchnic or pelvic ganglions. In some cord bladders, Braasch (quoting Koll) argues for dilatation of the ureter and pelvis, maintaining that atonic dilatation of the bladder is usually accompanied by dilatation of the ureteral meatus. Mathé, in a classification of the intrinsic causes of hydronephrosis, lists the neurogenic (neuromuscular, dysfunction, sympathetico-tonus) pathologic lesion as an etiologic factor. Elaborating on this he says that disease causing irritation or paralysis of the sympathetic splanchnic or pelvic ganglion, et cetera, can produce atonic changes in the pelvis resulting in hydronephrosis. Ward, Gask, and Ross, each report a case of hydro-ureter and hydronephrosis of neurogenic origin improved by presacral neurectomy.

INNERVATION OF URETER

Although the existence of a neuromuscular mechanism in the ureter has been definitely established by Maier, Macht, and other workers, Hryntschak, in 1925, challenged this view by denying the presence of the ganglion cells in the mucosa or muscularis of the upper two-thirds of the ureter in a large series of histologic sections.

Perhaps the best description of the nerve supply to the ureter is by Kuntz. Wharton, in 1932, carried out extensive microscopic dissections on stained histologic sections of fetuses, with the object of demonstrating the nerve supply of the ureter. This structure, like all hollow tube organs, has both intrinsic and extrinsic innervation.

Histologic dissection of the ureter discloses ganglion cells, medullated and non-medullated fibers within the wall. This neuromuscular system is probably the motive power of peristalsis. The extrinsic nerve supply, according to Wharton, is independent of that supplying the kidney and bladder. These nerves have their immediate origin from the renal ganglion and spermatic plexus, and from the abdominal sympathetic plexuses (aortic, hypogastric, and pelvic). Latarjet has demonstrated that the renal and abdominal sympathetics issue from the solar and celiac plexuses.

We have made a series of microscopic dissections of histologic

material employing Wharton's technique of procedure, and it is very satisfactory. Most of our dissections were on dogs and cats, and a few on fetuses. We used the Siehler stain which is almost specific for nerve tissue. Our anatomic dissections of the tissue to be studied included the peritoneum beyond that covering the ureter. We found that it was easier to dissect the nerves if the specimen was left in Siehler stain for forty-eight hours instead of twenty-four hours. These dissections demonstrated that the middle three-fifths of the ureter is relatively free of nerve fibers. In our dissections we traced the large nerve fibers issuing from the abdominal sympathetic plexuses, and as they approach the ureter they divide into smaller fibrils in a fan-like fashion, giving the impression that they end in the ureter. Since our dissections were more extensive, we picked up the ureter and could trace these fibers on their way to neighboring organs and structures. In their transit posteriorly to the ureter, they did send a few fibers to it.

We have observed that the proximal and distal ends of the ureter are abundantly innervated due perhaps to their proximity to plexuses. Whether this has any significance clinically is speculative. It is common knowledge that the middle part of the ureter is wider than the remaining portions. A much larger series of dissections will have to be done before any correlation with clinical material can be made. It is not definitely established what function these nerves serve. Ureteral denervation by Wharton and others has not resulted in any interference in urinary propulsion, or altered the lumen of the ureter and pelvis. Ureteral denervation has resulted in the relief of ureteral pain.

CLINICAL INVESTIGATIONS

In order to determine whether there were any structural and functional changes in the kidneys and ureters in patients with neurogenic or cord bladders, we studied a series of fifty cases. Forty-four of this group were patients with syphilis (spinal fluid Wassermann positive); the remaining six included patients with transection or tumor of the spinal cord; frontal lobe tumor, epilepsy, cerebral arteritis, and subarachnoid hemorrhage. We defined a bladder as neurogenic, where in the absence of any urethral obstruction the line on the graph definitely deviated from the normal, either toward a horizontal position (an atonic bladder), or

assumed a vertical direction (a hypertonic bladder). This definition is not a complete one, but was workable for our purpose. A cystometrographic study was made on each patient. In the series three were hypertonic, and the remainder were either hypotonic or atonic. The group composed of syphilitics was in the last classification, and this was further subdivided into the early preclinical hypotonic bladder, and the inert atonic bladder with long standing urinary retention, as evidenced by a flat curve. Approximately 50 per cent had a residual urine anywhere from 30 c.c. to almost complete retention. The early preclinical type of bladder comprised one-third (fifteen) of the syphilitic group, and because of their significant features they require some elaboration. The first desire to void was delayed in each case. The bladder capacity was greater than normal, with early evidence of flabbiness and loss of tone of muscular wall. A complete neurologic clinical examination failed to reveal any signs of nervous involvement. The spinal fluid Wassermann was positive. Ninety per cent of the luetic group studied showed hypotonic curves. The inference is that the bladder is perhaps the first structure to demonstrate the extension of the syphilitic lesion to the central nervous system.

Kidney function tests by the intramuscular phenolsulphonephthalein method were applied to the series, and contrary to Plaggemeyer's findings, we found no impairment of renal function. Visualization of the urinary tract was obtained by intravenous pyelography. This method was selected because it excluded the introduction of any artificial mechanical factor. It permitted us to study the kidney and ureter in their normal physiologic and dynamic states, and yielded functional data based on the time of excretion of the dye by the kidneys. One patient, an epileptic with an atonic bladder, was cystoscoped. The retrograde pyelograms revealed moderately dilated ureters but no hydronephrosis. Intravenous pyelography failed to confirm this finding. In the complete series of cases we found no evidence of dilatation of the ureter and renal pelvis. The rate of excretion of the dye was within normal limits.

The question of reflux of urine into the ureters has received a great deal of attention. Gruber, as the result of a series of experiments on animals concluded that the intravesical ureter served as a true valve, and complete excision of it leads to hydro-ureter and hydronephrosis. Braasch (quoting Koll) argues for regurgitation

of urine by means of a relaxation of the meatus which may easily accompany some cord bladders. We selected patients with cord bladders and a large residual urine for cystographic studies, to determine whether reflux could be obtained. The procedure adopted was to overdistend the bladder with 4 per cent sodium iodide, and then tilt the cystoscopy table with the head down. This failed to reveal any regurgitation of the dye into the ureter.

SUMMARY

1. It is apparently the common belief in urologic literature, that dilatation of the ureter and renal pelvis accompanies neurogenic and cord bladders.

2. Studies of the innervation of the ureter were done. These dissections demonstrated a relative lack of nerve fibers to the middle three-fifths of the ureter, as contrasted with the terminal portions.

3. Cystometrographic studies revealed that the earliest manifestation of syphilitic involvement of the nervous system is to be found in the bladder nerve mechanism.

4. We investigated fifty cases of neurogenic and cord bladders, and did not encounter a single case of dilatation of the ureter and renal pelvis. Renal function tests applied to the group demonstrated no impairment of function.

5. Further research in the field of anatomy and physiology of the upper urinary tract is indicated. Especially is this true today when surgery of the sympathetic system is receiving such widespread attention.

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ANURIA

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The generally accepted classification (Eisendrath[9]) of anuria divides the causes into prerenal, renal and postrenal; and the types into secretory, transitional and obstructive. The secretory type of anuria may have a prerenal or renal cause. The obstructive type is limited to those due to postrenal causes. Anurias due to occlusion of the conducting tubules of the kidney are designated as the transitional or combination group.

ANURIA OF THE SECRETORY TYPE WITH PRERENAL CAUSE

Anuria with the cause proximal to the kidney is relatively infrequent. This type may accompany dehydration, the result of prolonged emesis or diarrhea. Anuria may follow severe hemorrhage, or develop when there is a marked fall in blood pressure, as in shock, and occasionally it will be seen in advanced cardiac decompensation (Case 4). An oliguria of increasing severity most often will precede the cessation of urinary secretion in such diseases. Changes in the blood supply of the kidney, as in vascular spasm, embolism or thrombosis of the main renal vessels may be the cause. This type of anuria includes reflex anuria, the anuria occurring in hysteria, and anuria due to dysfunction of the endocrine system. True reflex anuria may be observed in unilateral urinary calculus (the other kidney being presumably normal), whether the stone is located in the kidney or the ureter. Also, it may be observed following treatment of diseases of the urethra, bladder or ureter, the inhibiting factor being trauma—as in dilation of urethral stricture or cystoscopy and ureteral catheterization. Reflex anuria probably occurs less frequently than is generally thought. Such a reflex disturbance of the secretory function of the kidney should be accepted as the cause of urinary suppression only after a most careful investigation. This is particularly true when it follows an operation on an organ such as the appendix or the gall bladder, disease of which may be confused with calculus or other disease of the kidney or ureter.

ANURIA OF THE SECRETORY TYPE WITH RENAL CAUSE

The secretory type of anuria, caused by intrarenal pathologic process, is an important clinical group and may occur in medical nephritis, nephrosis, suppurative nephritis, and in renal damage due to mercury, bismuth, arsenic and other heavy metals. It is observed in the toxemia of pregnancy, in pronounced jaundice, in carcinoma of the gall bladder, and in acute yellow atrophy of the liver. Ratliff[22] reported two cases of anuria in which a liver toxin was assumed to account for the renal changes. He calls attention to the importance of analysis of the blood for both urea and non-protein nitrogen. If the blood urea is relatively low these studies should be supplemented by blood sugar and amino acid determination. The finding of low or normal blood urea in anuria must mean that the liver function is practically absent. This would be confirmed by finding high blood amino acid and low blood glucose. In our case of acute yellow atrophy of the liver (Case 2), the patient died in uremia with blood non-protein nitrogen of 107 mgs. Unfortunately the blood urea and blood sugar were not run. Yet it suggests that hepatic toxin was the principal cause of the anuria. The secretory type of anuria may follow an operation upon the urogenital organs, in which case it will be caused by an acute renal infection or chronic renal disease. An anuria may occur where pre-operative studies have shown a normal kidney function and where no unusual operative difficulties have been encountered.

A fifty-nine-year-old man entered the hospital with partial urinary retention due to benign hypertrophy of the prostate. The blood pressure was 170/110. The urinary output was normal in amount, contained but a trace of albumin and the total phenolsulphonephthalein output for two hours was 60 per cent. X-ray and cystoscopic examinations were negative for calculus. Twenty-four hours after a suprapubic cystostomy preliminary to prostatectomy, he developed severe pain in both loins and oliguria, and on the sixth postoperative day there was a complete suppression of urine which persisted until death forty-eight hours later. A postmortem examination was not permitted but in the absence of fever and leukocytosis a diagnosis of anuria due to chronic renal disease was made. The extent of the kidney lesion had not been appreciated pre-operatively.

A postoperative anuria may be of short duration lasting but

twenty-four to thirty-six hours, when the amount of urine secreted will return to normal. The reëstablishment of the urinary output does not necessarily indicate a lessening of the gravity of the patient's condition as a corresponding improvement in the blood nitrogen retention may not occur. In a patient with a complete suppression of urine for thirty-six hours the non-protein nitrogen was 133 mgs. during the period of anuria. Following the cessation of the anuria the output of urine became normal within forty-eight hours, yet the patient died on the eleventh postoperative day with a blood non-protein nitrogen of 312 mgs. Autopsy disclosed an acute nephritis superimposed upon a chronic nephritis. A similar observation was made in a twenty-one-year-old woman (Case 1) with the history of an acute upper respiratory infection and surgical parotitis. Her body, following one injection of prontosil, had assumed a coppery red color. She was admitted to the hospital with anuria of thirty-six hours' duration and a non-protein nitrogen of 121 mgs. Four days later her urinary output was 54 ounces but the non-protein nitrogen was 200 mgs. The urinary output remained normal in amount until death which occurred fourteen days following hospital admission. At the time of her death the blood non-protein nitrogen was 303 mgs. Autopsy disclosed an acute nephritis.

Poisoning from mercuric chloride and arsenic is relatively frequent and these cases constitute an important group in secretory anuria from renal causes. Less frequently anuria may follow the administration of bismuth. McClendon[18] reports complete suppression of urine in two children following a single injection of bismuth in each case. One of his patients was a two-year-old child who was given 0.2 gm. of bismuth. The anuria lasted twenty-four hours. The second patient was a fifteen-months-old girl baby to whom was given 0.15 gm. of bismuth. Complete suppression of urine followed and lasted for forty-eight hours. Both patients recovered. Zimmerman[26] reports an anuria of five days' duration in a child one year old, following an injection of bismuth subsalicylate 0.3 gm. with recovery after decapsulation of the kidney. We have observed complete suppression of urine lasting eighteen hours in an eight-year-old female child who was given a single hypodermic injection of 0.3 gm. of bismuth because of a Vincent's infection of the gums. During the period of anuria

the non-protein nitrogen reached 101 mg. and the creatinine 4.4 mg. The abnormal nitrogen retention disappeared with the return of the normal urinary output. While the dose of bismuth was high for a child so young, probably of more importance in the development of the anuria was the history that four weeks prior to administration of the drug she had an acute illness, the diagnosis of which was acute bronchitis and sore throat. This illness, when viewed in retrospect, was probably a mild scarlet fever which had resulted in renal damage still present when the bismuth was given.

ANURIA OF THE TRANSITIONAL TYPE

The obstructive element enters into the development of the transitional type of anuria. It is to be distinguished from anuria of the obstructive type due to postrenal causes because frequently there is an existing renal disease which actively contributes to the transitional type of anuria. This type may follow a transfusion of blood; accompany hemoglobinuria; occur in dehydrated patients with a high fever; in potassium chlorate poisoning; or in the precipitation of the acetylated sulfonamides. In each instance there is an occlusion of the tubules of the kidney, the obstructing substance varying with its cause. The anuria following transfusion of blood is most often due to occlusion of the tubules with precipitated hemoglobin, and probably develops because of some incompatibility of the blood given. The presence of oliguria with high fever, nitrogen retention, and with varying degrees of acidosis should be regarded as a danger signal in giving a blood transfusion. Under such circumstances we have seen an anuria follow the eleventh blood transfusion in a thirty-two-year-old male patient, the donor having given blood on two previous occasions without untoward reaction. The anuria which occurred within a few hours after the last transfusion, persisted until death.

There may be some confusion as to the exact nature of the material obstructing the kidney tubules in these cases, as was true in the following instance. A four-year-old female child was admitted to the University Hospital with pneumonia for which she was given large doses of sulfapyradine. She recovered from this illness but was very emaciated when dismissed. Six days later she returned and died in the admitting room. The parents had observed that no urine had been voided for forty-eight hours before death.

At autopsy the renal tubules were found occluded with a crystalline substance. Acetyl sulfapyradine, the result of her previous medication, was suspected. Analysis proved that the crystals were urates and uric acid only.

In 1939 Tsao[33] and his co-workers reported a young male patient who had an occlusion of the kidney tubules following the use of one of the sulfonamide group of drugs. Many similar observations have been made by other workers since that date. While sulfapyradine seems to have the greatest tendency for crystalline formation, this may follow the administration of other members of the sulfonamide group of drugs. Reports indicate that sulfanilamide, sulfapyradine, sulfathiazole, sulfaguanidine and sulfadiazine, with slight variation in degree, are all capable of producing urinary concretions. Approximately 50 per cent of sulfapyradine is excreted as a relatively insoluble mono-acetyl derivative, which may accumulate in the tubules or ureters and result in obstruction of these structures and anuria. Emerson Smith[29] and co-workers believe that serious renal damage (other than crystalline formation) from sulfapyradine lacks confirmation; and Backhouse[1] concludes "the suppression of urine in the majority of cases of anuria associated with hematuria due to sulfapyradine, is largely a reflex phenomenon." Sadusk[26] and his co-workers, however, found "dilation of glomerular spaces and tubules, thickening of basement membranes or glomerular tufts, with changes in the shape of the capsular epithelium" in one patient who had been given large doses of sulfapyradine. They considered these changes the result of irritation from the drug.

OBSTRUCTIVE ANURIA

Anuria from postrenal causes is the result of an obstruction interfering with ureteral drainage. Its development and correction, in most instances, involve urologic problems only. It is this form of anuria which is most often reported by the urologist. Not infrequently, however, other causes of anuria may co-exist with postrenal obstruction. The ureteral obstruction may be due to calculus (approximately one-third of the cases are the result of stone), ureteral stricture, ureteral neoplasm, blood clots, malignancy of the bladder or pelvic genital organs, extrinsic pressure from a pelvic or abdominal mass, and surgical injury to the ureter. The ureteral

occlusion may be unilateral or bilateral. If unilateral, there may be only one kidney present, as a surgical or congenital single kidney; or the opposite kidney may be rudimentary, diseased, or possibly normal, when a true reflex anuria occurs. Further detailed discussion of obstructive anuria is unnecessary at this time. However, it should be emphasized that in the presence of anuria of uncertain cause, ureteral obstruction should always be eliminated. Reports of bilateral ureteral occlusion during the administration of the sulfonamide drugs have been sufficiently frequent that medication should be discontinued immediately in the presence of any evidence of renal irritation or appreciable decrease of urinary output. It would seem that hematuria and stone formation do not necessarily depend upon the size of the dose nor the number of crystals in the urine, but that an idiosyncrasy to this group of drugs may be present in certain individuals. There have been reports of the development of concretions in patients to whom only small quantities of the drug had been given, as was the case in one of our patients (Case 11). Occlusion of both ureters from this cause has also been reported in children.

SYMPTOMS

In anuria the total suppression of urine for days may be the only clinical evidence of existing disease. One of Myers'[20] patients had an anuria for thirty days before developing uremia. The secretory type of anuria is less likely to be accompanied by pain than is the obstructive type with a postrenal cause. Merklen,[17] in 1881, divided the symptoms of anuria into the period of tolerance and the period of intolerance or uremia. The relative duration of these two periods varies widely in different patients. Merklen states, "It is not unusual for a patient who has had complete suppression of urine for many days, to be up and about, eating and acting normally, having the appearance of perfect health." Behind this mask of well-being there is developing a uremia, the only evidence of which may be an early blood nitrogen retention. The early signs of the period of intolerance are blood nitrogen retention, headache, exhaustion and fatigue, insomnia, muscular twitching, dry tongue, occasional vomiting and hiccough. Symptoms indicating grave disturbance of the circulatory, digestive and nervous systems occur as the uremia advances. These in no way differ from those seen in uremia from other causes. Coma or delirium may precede death.

TREATMENT

The treatment of anuria due to prerenal or renal causes is largely limited to medical measures intended to stimulate urinary secretion, such as the introduction of fluids, transfusions of blood or plasma, counterirritants applied locally, diaphoretics, cathartics and diuretics. Renal decapsulation and blocking of the splanchnic sympathetic nerves have enthusiastic advocates. The prognosis in this type of anuria is more guarded than in that due to obstruction. In the latter, operative measures are indicated; frequently the cause of the anuria may be removed and the anuria relieved at once. In other instances diversion of the urinary stream proximal to the obstruction may be the prime necessity, maintaining this drainage until the emergency subsides. The obstruction is then removed as an elective procedure under more favorable circumstances. The treatment of anuria due to occlusion of the renal tubules is limited to forcing fluids (attempting thereby to flush the obstructing material from the renal tubules), and to the use of drugs which will correct an existing acidosis. Also, when the sulfonamides or other measures known to favor the development of this type of anuria are being employed, they should be stopped at once. The value of urea as a solvent for sulfonamide crystals has recently been demonstrated. Five grams dissolved in 150 c.c. of lemonade are given every four hours for six doses.

Fluids may be given orally by proctoclysis, hypodermoclysis, by duodenal tube, or intravenously, the last being the method of choice. When given intravenously the quantity varies from 50 c.c. to 1000 c.c. and the intervals from three to four hours with the smaller sized dose, to two or three times, each twenty-four hours when larger amounts are being given. To these may be added glucose or sucrose in from 5 to 50 per cent concentration, and sodium sulfate, 42.85 gms. per litre. The caution against giving sulfates with the sulfonamides because of the danger of the development of sulfhemoglobinuria should not be relaxed, yet the necessity for combating acidosis may, on occasions, justify disregardance of the usual contraindications. We have given sodium sulfate 42.85 gm. per litre in anuria with acidosis due to the sulfonamides on two occasions with no untoward reaction. Ringer's solution is frequently given. Alkalinization of the patient in existing or threatened acidosis may be accomplished by soda bicarbonate given oral-

ly or by proctoclysis, or by molar sodium lactate administered as follows: to each kilogram of body weight use 5 c.c. molar sodium lactate, 25 c.c. distilled water and 20 c.c. Ringer's solution. One-half of this amount is given intravenously, the remainder by hypodermoclysis. Dieckman[8] finds, when the emergency of the acidosis has been met in the above manner, the urine can be maintained alkaline by daily oral administration of 1 c.c. molar sodium lactate per kilogram of body weight.

Diuretin, when given intravenously, may stimulate the kidney to renewed activity and overcome an emergency. Sedatives should be given with caution in anuria. However, stimulants such as caffeine sodium benzoate may be indicated and prove of value. Renal function may be encouraged by continuous bladder or ureteral catheter drainage with vesical or pelvic lavage, at two to four-hour intervals, with a warm sterile solution. If too much fluid is given, edema which is not an infrequent finding, the result of anuria, may occur, especially pulmonary edema. When there is beginning return of urinary secretion following an anuria, the fluids given each twenty-four hours should not as a rule exceed the output of urine by more than 50 per cent. Under these circumstances it will often be better to give the fluids in smaller amounts at six to eight-hour intervals. In general, the electrolytic solutions, the chlorides and sulfates, are indicated, especially in anuria accompanying dehydration, massive hemorrhage, and the like; but should be given with care in anuria due to renal damage. Here glucose, sucrose, and Ringer's solution are especially indicated. While glucose may be inferior in its diuretic action to sucrose, it has a much greater food value, as the renal threshold for the former is 180 mg. per cent, while it is zero for sucrose. Acacia has no rational use in complete suppression of urine.

Either independently, as in anuria from prerenal or renal causes, or as an adjuvant to surgical treatment of an obstructive anuria, when a reflex anuria remains, paravertebral blocking of the splanchnic sympathetic nerves *may* result in relief of the anuria. Eisendrath quotes Rubeitius to the effect that this measure had been successfully used in seven out of eight cases. We have used splanchnic block only once in the treatment of anuria, and without apparent beneficial results.

Renal decapsulation may be considered in anuria from nephrosis,

renal necrosis, acute glomerular nephritis, especially in children, and in chronic glomerulo-nephritis. It is of doubtful value in anuria due to mercuric chloride poisoning.

Ureteral catheterization with maintenance of urinary drainage, ureterostomy, pyelostomy or nephrostomy, unilateral or bilateral, may be necessary in anuria due to ureteral obstruction. Frequently these surgical procedures assume emergency importance and should not be delayed. Later removal of the obstruction by ureterolithotomy, pyelolithotomy or by the restoration of the ureteral channel in surgical injuries due to accidental ligation, et cetera, may be undertaken as an interval procedure after urinary secretion has been fully reëstablished.

Prompt and vigorous treatment of anuria as soon as recognized is essential. Delay lessens the chance of the reëstablishment of normal urinary secretion and recovery. Repeated analysis of the blood for nitrogen, chlorides and CO_2 combining power are essential in promotion of treatment in the individual case.

CASE REPORTS

Case 1.—(Renal) Uremia After Suppurative Parotitis.

L. G. A., female, aged twenty-one, was admitted to the Methodist Hospital, June 22, 1939, with a temperature of 102, a white blood count of 21,450; an enlarged and tender right kidney, dry tongue, stupor, and anuria of thirty-six hours' duration. Radiographs gave no evidence of renal stones. The non-protein nitrogen was 121 mg., creatinine 7.2 mg., sulfanilamide 1.2 mg. per 100 c.c. (after prontosil). Despite five blood transfusions of 500 c.c. each, given every second day; daily intravenous fluids, sodium sulfate 42.85 gm. per litre of water, the non-protein nitrogen gradually rose to 303 mgs. and the creatinine to 12.9 mg. per 100 c.c. at the time of death on the nineteenth day after admission. Autopsy disclosed acute nephritis.

Case 2.—Anuria Following Operation on the Gall Bladder Suggesting the Presence of the Hepato-Renal Syndrome.

N. C., male, aged sixty-six, was admitted to the hospital on March 31, 1940, and died April 25, 1940. A diagnosis was made of acute yellow atrophy of the liver with chronic hepatitis. On admission to the hospital the temperature was 100, respiration 20, and pulse 99, with blood pressure of 120/68. There had been a loss of weight of 30 pounds in three months. The patient was dyspeptic and jaundiced. Radiograph showed a nonfunctioning gall bladder, but no evidence of renal or biliary calculi. The patient was given 1000 c.c. normal salt solution alternating with distilled water with 5 per cent glucose twice daily, in ad-

dition to fluids by mouth. The average intake of fluids was 2200 c.c. daily and the daily output of urine averaged 1300 c.c. On April 17, 1940, an exploratory operation was done by Dr. W. D. Gatch, with negative findings for kidney, pancreas, duodenum, stomach and intestines. The liver was one-third normal size. It was dark colored, firm, and the edge was rounded. There were no stones in the gall bladder. The bile was white. The gall bladder was drained. Following operation there was no urine secreted the first twenty-four hours. Three blood transfusions of 500 c.c. each, and two daily intravenous injections of 500 c.c. each of normal salt solution or distilled water and glucose were given; also Baxter's solution 5 per cent dextrose, et cetera, averaging 1850 c.c. each twenty-four hours; also adrenalin 5 minims every two hours for ten doses. The urine output on the second day after operation was 165 c.c., and from then on, 30, 15, and 10 c.c. to none. The non-protein nitrogen rose to 107 mg. and the patient died in uremia on the eighth day postoperative.

Case 3.—Renal and Postrenal Anuria in Myelogenous Leukemia and Chronic Nephritis.

G. G., male, aged seventy-two, was admitted to hospital on October 24, 1941, with a history of gradual loss of weight and weakness during the past year. There was a nocturia of two times. The spleen and liver were palpable. The blood count showed—hemoglobin 29 per cent; red blood cells 2,120,000; white blood cells 64,000; polynuclears 27; myelocytes 65. Blood transfusions of 500 c.c. each were given on October 25, 27 and 31; also x-ray therapy. On November 3, 1941, the patient passed a kidney stone. On November 8 he became anuric, with a non-protein nitrogen of 115 mg. and blood pressure of 150/60. On November 11 there was total anuria with bounding pulse and twitching of muscles. A blood transfusion of 650 c.c. was given. Cystoscopy (the patient comatose) showed multiple small stones in the bladder. Both ureters were obstructed but finally the left catheter was passed and anchored. On November 12 the patient's condition remained unchanged except for the abundant flow of urine from the left ureter catheter. On this date the non-protein nitrogen was 127 mg. and the creatinine 11.6 mg. On November 13 the non-protein nitrogen was 126 mg. and the creatinine 8.8 mg. On November 14, the day of death, the non-protein nitrogen was 137.5 mg., the creatinine 10.8 mg. and the blood pressure 160/64.

Case 4.—Prerenal Anuria of Three Days' Duration in a Patient with Mitral Stenosis. Recovery.

M. C., female, aged twenty-eight, was admitted to the hospital on August 15, 1934, with anuria, shortness of breath, and edema of the extremities and abdomen. Three years of ill health had followed rheumatic fever. Examination disclosed mitral stenosis, enlarged liver, pleural effusion and mild toxic goiter. The blood non-protein nitrogen

was 84 mg. per 100 c.c. Cystoscopy showed patent ureters. The pyelograms were normal. Treatment consisting of intravenous fluids and digitalis was given. Thoracocentesis was repeated every ten days. This was followed by a gradual decrease of edema. A small amount of urine was secreted on the third day, and this increased in amount day by day. The patient was dismissed at the end of the sixth week much improved.

Case 5.—Anuria Following Acute Infection of the Throat with Probable Meningitis.

G. B., male, aged thirty-six, after three weeks of recurring throat infection and fever, during which time he had taken large amounts of sulfathiazole, had a chill followed by fever of 103 and delirium the next day. On April 30, 1942, he was admitted to the Methodist Hospital with a temperature of 104 and in a comatose state which had existed for twelve hours. His throat was acutely red, the abdomen was distended, and a generalized papular eruption of the skin was present. No urine had been voided for sixteen hours. He was catheterized of 3.5 ounces of urine which showed a specific gravity of 1.018, a trace of albumin, and no sugar; and on microscopic examination, many pus and blood cells. The temperature rose to 106. The white blood count was 26,700; the non-protein nitrogen was 55.4 mg. CO_2 51 vols. per cent, and sulfathiazole 3.5 mg. per cent in the blood. Blood cultures were negative. The spinal fluid findings were negative. Medication consisted of sedation and intravenous fluids with glucose every eight hours, also with the addition of sulfadiazine, aminophyllin, concentrated glucose and sodium sulfate. On May 1, 1942, after a total anuria of twenty-nine hours a cystoscopic examination was made and the ureters were catheterized. There was no ureteral obstruction and no residual urine in the bladder or kidney pelves. Pelvic lavage was given and the bladder drained by an indwelling catheter. At six o'clock that evening there was a half ounce of urine, and on the following days 9, 18, 29, 33 and 33 ounces. The patient remained semicomatose and delirious and had one convulsion. There was swelling of the right hand and right ankle, and spastic paralysis of the right arm and leg. On May 2, 1942, the blood non-protein nitrogen was 101.5 mg., the sulfadiazine 31 mg. per 100 c.c.; and 39.3 CO_2 vols. per cent. On May 4 the non-protein nitrogen was 134 mg., the sulfadiazine 22.7 mg. CO_2 38.1 vols. per cent. On May 5, the non-protein nitrogen was 150 mg., the creatinine 12 mg. No urine was excreted during the twenty-four hours preceding his death on May 7. No autopsy could be obtained.

Case 6.—Sepsis, Anuria (Secretory Type) and Elevated Blood Chemistry Following Cesarean Section.

Mrs. H., aged thirty, developed septic temperature, drowsiness, scanty urine and elevated blood chemistry a few days after cesarean sec-

tion. The blood non-protein nitrogen rose to 141 mg. and the creatinine to 9.2 mg. per 100 c.c. Ureter catheter drainage, intravenous fluids, brought gradual improvement with normal output of urine, normal temperature and normal blood chemistry by the end of the fourth week. During the early part of her illness there was advanced oliguria with a question of renal or postrenal anuria developing. The ureters were catheterized and no obstruction found. The patient recovered under intravenous glucose with distilled water, et cetera.

Case 7.—Renal Anuria Due to Nephritis Following Respiratory Infection.

C. S., female, aged twenty-three, was admitted to the hospital April 26, 1929, with headache, backache, sore throat, coryza, elevated temperature and anuria. The phenolsulphonephthalein kidney function test was 12 per cent for two hours. The non-protein nitrogen was 86 mg., the creatinine 3.8 mg. per 100 c.c. of blood. The daily output of urine was as follows; April 26—none, April 27—none, April 28—10.5 ounces, April 29—19 ounces, with non-protein nitrogen 85.6 mg. and creatinine 8.1 mg.; April 30—26 ounces, May 1—48 ounces; the non-protein nitrogen 104 mg. and creatinine 8.4 mg. Therapy consisted of mustard drafts to the loins, salicylates, fluids, laxatives, enemas, et cetera. Gradual improvement with a return to normal urinary output and normal blood chemistry marked the progress of the remainder of her stay in the hospital. Recovery.

Case 8.—(Renal) Anuria Following Bichloride of Mercury. Decapsulation of Kidneys. Died.

M. M., male, aged twenty-nine. Within one-half hour after taking, with suicidal intent, 50 grains of bichloride of mercury, the patient was admitted to the hospital in a semi-comatose condition. His temperature was 97.2 and blood pressure 65/40. The urine, scanty in amount, showed many blood cells and casts. After gastric lavage, forced fluids were given by mouth and intravenously. On April 23, 1932, secretion of urine had ceased. The non-protein nitrogen was 95 mg., creatinine 6.4 mg. per 100 c.c. of blood. On April 26, bilateral renal decapsulation was done. The kidneys were not enlarged but tense and firm. There was no necrosis. The areolar tissue about the kidneys was surcharged with fluid. Several hours after operation catheterization obtained 6 ounces of bloody urine which was loaded with blood cells and casts, and contained 0.2 per cent urea. The catheter was anchored and hot bladder irrigations were ordered. The dressings were saturated with fluid. On April 28, 1932, his condition was growing worse; 8 ounces of urine being secreted in twenty-four hours; a large necrotic area appeared in the mouth, and edema of the face and drowsiness increased. The blood count showed hemoglobin 64; red blood cells 2,890,000; white blood cells 13,400; and the blood pressure was 160/90. On April 29, the non-protein nitrogen was 129.5 mg. and 12 ounces

of urine were secreted in twenty-four hours. On May 3 there were 32 ounces of urine, and on May 4—32 ounces. On May 6 the non-protein nitrogen was 200 mg., creatinine 15.6 mg., urine acid 9.8 mg., urea 342 mg., blood sugar 150 mg., per 100 c.c. On May 8 the patient was vomiting, and on May 9 there was some infection in the kidney wounds. On May 10 the temperature fluctuated from normal to 101°, and 14 ounces of urine were secreted. The patient was hiccoughing. On May 11 a transfusion of 600 c.c. was given. On May 12 the patient had pleurisy and the urine was scanty. On May 13 the patient had a cough and bloody sputum, and no urine was secreted. On May 14 the non-protein nitrogen was 273 mg. and on May 16 the patient was semi-comatose, and died the following day. Autopsy showed mercurial nephritis with suppuration, gastro-enteritis, and bronchopneumonia.

Case 9.—(Renal) Anuria Due to Bichloride of Mercury Poisoning. Decapsulation of Kidney. Died.

V. B., female, aged twenty-seven, on April 3, 1934, at 10:30 p.m., swallowed 18 grains of bichloride of mercury. Within an hour the patient was admitted to the hospital where appropriate emergency treatment was instituted, including gastric lavage, alkalies and intravenous fluids. A catheter was anchored but no urine was secreted at any time. On April 4, the patient was very tender over the upper abdomen and the region of the kidneys. Her temperature was 98, and the blood count showed—hemoglobin 69 per cent; red blood cells 3,710,000; white blood cells 27,000; the blood pressure was 120/90 and the blood non-protein nitrogen 100 mg. per 100 c.c. On April 6 chlorides were 410 mg., calcium 8.0 mg., non-protein nitrogen 105.5 mg. per 100 c.c. On this date unilateral right renal decapsulation was done. The patient was considered a serious anesthetic risk—the pulse 160. She was drowsy, sore and tender. On April 7, 1934, the non-protein nitrogen was 121 mg. The patient died at 6:36 p.m. Autopsy showed bichloride poisoning, acute nephritis, superimposed upon chronic nephritis.

Case 10.—(Renal) Anuria Accompanied by High Blood Creatinine Following the Use of a Mouth Wash of Salvarsan. Recovery.

G. W., female, aged nineteen, was admitted to hospital on November 17, 1932, and was dismissed December 10, 1932. Following extraction of a tooth two weeks previously, she had used twice daily a mouth wash of salvarsan for trench mouth. Nausea and vomiting continued for five days. The white blood count was 12,300; the urine scanty, and the phenolsulphonephthalein kidney function test was zero. The daily twenty-four hour output of urine varied as follows: 8, 6, 0, 6, 5, 8, 16, 69, 83, 97, 100, 103, 106, and 91 ounces.

Blood chemistry every second day. Non-protein nitrogen was 158, 159.5, 125, 121, 97.3, 68.8, 54.6, 40.6, 31.6. Creatinine 16.4, 16.8, 14.4, 10.8, 8.0, 6.4, 4.5, 2.8, 1.6. Therapy consisted essentially of sympto-

matic relief—cathartics, enemas, hypertonic glucose, fluids and sedation. One blood transfusion of 500 c.c. was given.

Case 11.—(Renal) Anuria, Transitional Type, Following Sulfathiazole. Relieved by Ureter Catheter Drainage and Forced Fluids.

M. M., female, aged seventy-nine, with perirectal abscess, after receiving 9 gm. sulfathiazole in two days, passed bloody urine followed by urinary suppression for four days. Both ureters were catheterized and the catheters anchored. After hot irrigations of the kidneys and intravenous fluids, 50 c.c. of urine was secreted in twenty-four hours, with gradual increase to normal in a week. The non-protein nitrogen rose to 88 mg. and the creatinine to 9.3 mg. per 100 c.c. Analysis of the segregated urines showed acetylated sulfathiazole, left 4.7 mg. and right 3.2 mg. per 100 c.c.

Case 12.—(Postrenal) Anuria Due to Bilateral Ureteral Block Following the Administration of Sulfapyradine for Chronic Bronchitis.

S. M., male, aged fifty-four, was admitted to the hospital February 28, 1940, and was dismissed March 9, 1940. On admission, the patient's temperature, pulse, respiration, blood pressure and blood count were within normal limits. The voided urine, scanty in amount, was red, cloudy, alkaline, specific gravity 1.015, albumen 10 per cent, sugar negative, 2x pus, and loaded with blood cells. Radiographs revealed no calculi. Intravenous fluids and glucose were given. On February 29, the non-protein nitrogen was 45 mg. and the creatinine 2.8 mg. The bladder was catheterized and no urine was obtained. Cystoscopy at 5:30 p.m. on this date (no urine secreted as yet, and the patient hiccoughing for three or four hours) detected no urethral obstruction. The bladder medium was cloudy but not bloody. There was slight edema of both ureteral orifices. Emanating from each were crystal-like bodies in string-like formation. When these were dislodged from the right orifice and the catheter entered, there was a continuous efflux of dark red grumous material in ribbon formation. There was no obstruction in the right ureter. In the right pelvis, 30 c.c. smoky residual urine was found. The catheter was retained. On the left there was difficulty at the orifice, but finally a No. 4 bougie passed and the same material extruded as was observed on the right side. There was no obstruction in the left ureter above the orifice. The bougie was anchored, also a urethral catheter. The urine obtained on February 29 (residual from right kidney) showed acetylsulfapyradine 186 mg. On catheter drainage, forced fluids and glucose the quantity of urine promptly returned to normal. On March 1 the phenolsulphonephthalein kidney function test showed a total for the two hours, 165 c.c. and 46 per cent. On March 7 the voided urine was slightly cloudy, specific gravity 1.010, albumen x, sugar negative, urea 1 per cent, pus cells x, blood cells occasional.

Case 13.—(Postrenal) Anuria of Thirty Hours Due to Stone in Single Kidney (Surgical). Relieved by nephrostomy but patient succumbed on eighteenth day postoperative.

J. G., male, aged forty-eight, with a calculus the size of a hazelnut in the lower calyx of the right kidney, and left calculus pyonephrosis, had a left nephrectomy on February 1, 1925. At this time the phenolsulphonephthalein elimination was 79 per cent in two hours and the blood non-protein nitrogen was 26.4 mg. per 100 c.c. Eight years later, June 10, 1933, he was re-admitted to the hospital with cloudy urine, a blood pressure of 134/64, a phenolsulphonephthalein elimination of 60 per cent for two hours, and a blood non-protein nitrogen of 33 mg. X-ray examination showed a stone in the lower calyx of the right kidney and a small stone in the remaining portion of the left ureter. Operation was refused. He was again re-admitted on August 30, 1933, with a temperature of 101.2 and a blood pressure of 130/60. The blood count showed—hemoglobin 90 per cent; red blood cells 4,560,000; white blood cells 16,400; and blood non-protein nitrogen 65.5 mg. per 100 c.c., the patient having passed no urine for thirty hours. The right ureter was catheterized and several cubic centimeters of purulent urine obtained. The catheter was anchored and hot irrigations ordered. Later in the day, with a temperature of 105 and delirium, the patient got out of bed, displacing the catheter. Normal salt solution (1500 c.c.) was given intravenously and the ureter catheter replaced. The urine, which at first was purulent, cleared and increased in amount under daily intravenous fluids and glucose. On September 11, 1935, the patient's condition being somewhat improved, the stone was removed from the right kidney (now pyonephrotic), by pyelolithotomy, and nephrostomy drainage instituted. The drainage of urine was adequate and progress satisfactory until the patient suddenly developed pneumonia and died on the eighteenth postoperative day.

Case 14.—(Postrenal) Anuria Due to Stone in Single Kidney (Surgical). Relieved by nephrolithotomy and nephrostomy.

A. M., female, aged thirty-four. A left nephrectomy was done May 17, 1929, following a diagnosis of calculous pyonephrosis and tuberculosis. Prior to nephrectomy the right kidney was normal to all laboratory tests and pyelography. The blood pressure was 110/60; the blood non-protein nitrogen 28.9 mg. and creatinine 1.5 mg per 100 c.c. The wound healed promptly and the patient gained 50 pounds in five months. She then developed pain in the right loin with cloudy urine. Radiographs on November 16, 1929, showed the right kidney pelvis filled with stone (an exact duplication of the right pyelograms of May 10, 1929). She was re-admitted to the hospital February 16, 1930, with anuria of forty-eight hours' duration. The temperature was 100, white blood count 17,000, blood pressure 142/50, and blood non-protein, nitrogen 68 mgs. per 100 c.c. She had no pain or discomfort and no desire to void. Her tongue was clean and moist. At cystoscopy we

failed to catheterize the right ureter. On February 17, 1930, nephrolithotomy with nephrostomy drainage was performed. Soft stony material was removed from the kidney pelvis. At 9:00 p.m. the dressings were saturated with urine. On February 18, in the morning the temperature was down, the pulse 95 to 100, the tongue moist, and the dressings wet with urine. In the afternoon she had hiccough for several hours and occasional vomiting. Forced fluids were given intravenously and by proctoclysis. By February 24, 1930, the impending uremia of six days before seemed postponed. The dressings were saturated with urine but there was none from the bladder. Cystoscopy encountered an obstruction in the right ureter but a No. 6 catheter was finally passed and retained. Temporarily progress was more satisfactory. On April 17, 1930, the patient was sent home with nephrostomy drainage, which was continued until death on February 15, 1932.

Case 15.—(Postrenal) Anuria due to Stone Obstruction Right (Single) Kidney, the Other Having Been Removed.

H. K., male, twenty-six, was admitted to the Methodist Hospital August 21, 1920. He had had a left pyelolithotomy in January, 1919, a left nephrotomy in March, 1920, and left nephrectomy in April, 1920, because of hemorrhage and infection. A right renal colic occurred on August 12, 1920, and recurred in the early morning of August 20. Two ounces of urine was voided at 4:00 a.m. No more urine was voided or obtained by catheter until August 23, when, after a purge and forced fluids, he voided 50 ounces in the twenty-four-hour period. The blood urea was 128 mg., creatinine 2.5 mg. per 100 c.c. The phenolsulphonephthalein elimination was 27 per cent in two hours. On August 31, 1920, the blood urea was 35 mg., the creatinine 2.6 mg. per 100 c.c. and the phenolsulphonephthalein output 40 per cent in two hours. Radiographs showed a hazelnut sized stone in the right kidney pelvis which was removed later by pyelotomy.

Case 16.—(Postrenal) Anuria of Eighteen Hours' Duration due to a Calculus in a Solitary Kidney. Relieved by ureter catheter drainage. The use of avertin injected into the ureter probably materially facilitated the passage of the stone.

W. C., male, aged sixty-three, whose right kidney had been removed in 1932 for calculus pyonephrosis, was admitted to the hospital November 5, 1940, with pain in the left abdomen and anuria of eighteen hours' duration. The temperature was 100, blood count normal and blood pressure 133/84. The non-protein nitrogen was 79 mg. per 100 c.c. Intravenous fluids and glucose were given and a catheter was anchored. The output of urine was 2 ounces in twenty-four hours. The pain continued, accompanied by nausea and vomiting. Cystoscopy met an obstruction in the left ureter at 2 inches from the bladder. A No. 4 bougie and a No. 4 catheter were passed and left indwelling. Copious drainage of urine followed. The phenolsulphone-

phthalein kidney function test rose to 50 per cent in two hours, and the non-protein nitrogen fell to 35.7 mgs. per 100 c.c. On November 22, 1940, 15 c.c. of 2 per cent avertin was injected into the left kidney pelvis and the catheters were removed. The ureteral stone promptly passed into the bladder and was removed with the cystoscopic rongeur.

Case 17.—(Postrenal) Anuria due to Calculus in Single Kidney (Surgical).

L. C., male, aged twenty-four, was admitted to the Methodist Hospital on September 19, 1922, with right renal colic due to a calculus in a solitary right kidney (the left kidney having been removed in August, 1921). The phenolsulphonephthalein kidney function test was 22 per cent, the non-protein nitrogen 27.6 mg. and creatinine 3.1 mg. On September 12, 1922, he had a colic. Radiograph showed a small stone half-way down the right ureter. An anuria of eighteen hours was relieved by ureter catheterization which pushed the stone into the kidney pelvis. On October 22, 1922, the ureter again became blocked. A ureteral catheter was again passed and retained several days. The phenolsulphonephthalein kidney function test remained at 20 per cent for two hours. On November 3, 1922, the patient was dismissed, assuming that the stone would pass spontaneously. On November 6, 1922, he was re-admitted to the hospital with renal retention. Ureter catheter drainage was repeated. Phenolsulphonephthalein elimination tests showed fluctuation of function from 10 to 50 per cent in two-hour tests. On November 29, 1922, a combined pyelotomy and nephrotomy and exploration of the kidney was done. Shock necessitated termination of operation without finding the stone. The patient died uremic on December 10, 1922.

Case 18.—Anuria of Four Days' Duration due to Bilateral Renal Calculi.

N. J. C., male, aged sixty, had received an x-ray diagnosis of bilateral renal stones eight years before. For two months before admission to the hospital, the urinary stream became smaller and less forceful until no urine was passed. The patient had no pain, no desire to void and only slight tenderness in the left loin. He had a temperature of 99, and blood pressure of 155/90. The non-protein nitrogen was 71.4 mg. and creatinine 4 mg. per 100 c.c. The white blood count was 14,350. The patient was feeling well. Radiographs showed a small stone in the right kidney pelvis and a left ureteral stone 4 inches from the bladder. Ureteral catheterization obtained purulent urine from both kidneys. The catheters were left indwelling. Drainage, intravenous fluids, et cetera, brought relief and the urinary output and blood chemistry gradually became normal. Six months later the patient passed a stone after a right renal colic, and another a few days later after a left renal colic.

Case 19.—Reflex (?) Anuria in Bilateral Urinary Calculus.

F. B., male, aged forty-two, was admitted to the Methodist Hospital September 14, 1939, complaining of nausea and vomiting of two weeks' duration and anuria of fifty-two hours' duration. No urine was obtained by catheterization of the bladder. The abdomen was distended. There was tenderness in the loins. Radiographs showed a branched stone in the left kidney pelvis and a large stone in the lower right ureter. Normal salt solution (1000 c.c.) was given by hypodermoclysis and heat was applied to the loins. The following day the urinary output was 975 c.c. and the next day 6600 c.c. From that time on the daily excretion of urine was from 1500 to 2000 c.c. On admission the non-protein nitrogen was 60 mg. per 100 c.c.; the white blood count 15,400. On September 9, 1921, the phenolsulphonephthalein kidney function test was 55 per cent for two hours, and the blood non-protein nitrogen was 31.6 mg. per 100 c.c. Under forced fluids and urinary antiseptics the temperature became normal and the nausea subsided. On October 21, 1939, a right uretero-lithotomy through an extraperitoneal iliac incision was done. The stone was 1⅛ inches long and ⅜ inch across. Urine drained freely from the wound but none from the bladder for the next two or three days. As the wound drainage decreased, more urine was voided until none came through the incision. This gave the impression that the left kidney was functionless, but on November 8, when the ureters were catheterized, the rate of flow from the left equaled that from the right. Indigo carmine appeared in three minutes from the right and in five minutes from the left. It is assumed that suppression of secretion from the left kidney following operation upon the right ureter was due to reflex causes. On December 5, 1929, a left pyelolithotomy was done with uneventful recovery. Radiograph taken August 29, 1930, showed recurrence of a large branched stone in the left kidney and none in the right. The phenolsulphonephthalein kidney function test was 70 per cent for two hours, the non-protein nitrogen was 28.5 mg. and the blood pressure 169/98.

Case 20.—(Postrenal) Anuria Following Cystoscopy and Ureteral Catheterization in a Case of Unilateral Stone. (Seen in consultation with Dr. P. E. McCown.) Reflex inhibition of urinary secretion in this case has some support.

R. T. M., male, aged forty-seven, had right renal colic of one week's duration. The urinalysis was negative, the blood pressure 155/90 and the phenolsulphonephthalein renal function test 39 per cent for two hours. Cystoscopy and radiographs disclosed a stone in the lower right ureter. A catheter was passed on the left and was followed by pain throughout the abdomen, also a dry tongue. At a second cystoscopy the left ureter was again catheterized. The right was still obstructed. Indigo carmine appeared in five minutes from the left and none after thirty minutes from the right. The left pyelo-

gram was normal. Following this cystoscopy the secretion of urine ceased for two days, though the patient received 6000 c.c. of fluids by mouth and intravenously. The non-protein nitrogen rose to 70 mgs. per 100 c.c. The blood pressure was 170/100 and the temperature 100. He was again cystoscoped and the left ureter catheter left indwelling. Urine which at first was scanty, increased gradually to normal within a week. The right ureteral calculus passed spontaneously soon after dismissal.

Case 21.—(Renal) Anuria Following Prostatic Resection.

T. B., male, aged sixty-seven, with partial retention of urine and blood pressure of 165/90, a phenolsulphonephthalein output of 62 per cent in two hours, and negative x-rays, was operated upon by prostatic resection on March 12, 1936. He was dismissed on the eighteenth day with three-fourths ounce of residual urine. He continued to have a cloudy urine, nocturia two to three times, and one-half ounce to an ounce and a half of residual urine. Cystoscopy showed remaining hypertrophied prostatic tissue. He was re-admitted to the hospital on November 10, 1936, when his blood pressure was 190/118 and the phenolsulphonephthalein elimination was 68 per cent for two hours. The prostate was again resected the following day. Very little urine (3 or 4 ounces) was excreted during the first post-operative day and none afterwards. Forced fluids by mouth and intravenously with glucose; inductothermy through both kidneys, novocain, paravertebral block, and hot fomentations to the loins, failed to relieve. Uremia gradually became more profound. The non-protein nitrogen, which was 75 mg. on the second day of anuria, gradually rose to 252 mg. and the creatinine to 20.8 mg. per 100 c.c. of blood on the day of death, November 24, 1936, the twelfth day of anuria.

Case 22.—Renal Anuria in a Child of Five Years due to Nephritis following Acute Middle Ear Infection.

B. J., female, aged five, was admitted to the hospital December 7, 1941, because of abdominal pain, vomiting and anuria of three days' duration. Two weeks previously the child had an upper respiratory infection culminating in an acute middle ear condition, which drained pus two or three days. She was given sulfanilamide in 5 grain dose three times daily for three days. After this she was much improved. Four days later she developed pain in the abdomen and loins, vomiting and anuria. Temperature was 100 degrees and the white blood count 11,000.

Treatment consisted of intravenous injection of normal salt solution and 5 per cent glucose 500 c.c. daily with retention enemas of tap water and nembutal as a sedative to control vomiting. On the second day in the hospital the child was given 750 c.c. of 10 per cent glucose in normal salt solution without enemas. Only a teaspoonful of urine showed 4 per cent albumin, numerous casts, much pus and many red

blood cells. The systolic blood pressure varied from 110 to 130. Edema of the face, feet and hands was present.

Treatment by forced fluid and glucose, hot applications to the abdomen and loins and diuretics failed to relieve the anuria. The patient died uremic on the fourteenth day in the hospital and the seventeenth day of anuria.

RESUME

Twenty-two cases of anuria are reported. Of these, four followed surgical operations; two followed acute respiratory infection; two were due to bichloride poisoning. Four followed medication as follows: two due to sulfonamides, one to bismuth, and one to salvarsan.

There were eight cases of urinary calculus; five due to stone in (surgical) solitary kidneys; two to bilateral renal calculus and one due to unilateral renal calculus. One occurred in leukemia and one in cardiac decompensation due to mitral stenosis.

Three of the four patients who had anuria following surgical operations died, as did also the one due to leukemia, the two due to acute respiratory infection, and the two who had bichloride poisoning. All of these belong in the classification of renal anuria.

In the eight cases of anuria due to urinary calculus only one patient died.

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PANCREATIC LESIONS CONFUSING UROLOGIC DIAGNOSIS

REPORT OF THREE CASES

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Because the pancreas is a retroperitoneal organ lying across the upper abdomen with its head in close relationship to the right renal fossa and its tail to the left, it is easy to see how lesions of the pancreas might be confused with renal lesions.

Surgical lesions of the pancreas are not uncommon, but instances in which they have been confused with renal lesions are rare. Walters states that 254 patients with conditions requiring surgery of the pancreas were seen at the Mayo Clinic over a five-year period. Of these, 185 had malignant lesions and sixty benign lesions. The benign conditions in order of frequency were: pancreatitis, acute and chronic; cysts; accessory pancreas; adenoma; hyperinsulinism; pancreatic lithiasis; necrosis.

Walters mentions the possibility of renal stone being confused with acute pancreatitis. We have never seen an instance of either condition in which such confusion was of any duration or required the application of any special diagnostic procedures, nor have we found any such case described in the literature.

We have, however, recently seen a patient who had been subjected to cystoscopy and pyelography on account of a pain in the upper abdomen and left side of the back. Some days later, while under our observation, the pain became suddenly very severe and was thought to be due to either acute pancreatitis or perforated ulcer, proving to be the latter.

Malignant tumors of the pancreas are usually small, and no instance of confusion with renal tumor has come to our attention. All of the instances of real confusion in diagnosis seen by us, and all but one of the few cases reported in the literature, were due to cysts—and this is what would be expected.

Thigpen divides pancreatic cysts into five groups:

1. *Pseudocysts.* These are cysts without any epithelial lining and may be the result of trauma or inflammation.

2. *Retention cysts*
3. *Neoplastic cysts.*
4. *Cysts resulting from defective development*
5. *Parasitic cysts* (hydatid, et cetera)

Cysts are usually smooth, tense and circumscribed, present in the upper part of the abdomen, most often on the left side and very occasionally below the navel. Most of them cause pain in the left epigastrium, extending into the back.

We wish to report three instances of confusion in diagnosis caused by pancreatic lesions and to give a brief discussion of other cases reported in the literature.

Case 1.—B. L., a colored housewife of thirty-five, was first seen on May 5, 1941, with complaints of generalized aching, particularly dull aching pain in the right upper quadrant and back. The pain was of two months' duration, and was not associated with any digestive disturbance or bowel action. The appetite was good, and she was able to eat all types of food. Cardio-respiratory and genito-urinary history was not remarkable. Previous operations were salpingo-oöphorectomy in 1927 and tonsillectomy in 1933. There had been no pregnancies, and no menses since 1927. The past history was not unusual in other respects. Physical examination at this time revealed a well developed, obese negress of thirty-five, weight 228 pounds. The head and neck were not remarkable. The chest was clear to percussion and auscultation. The heart was not enlarged, the sounds of good quality. The blood pressure was 110/80. In the abdomen a mass could be felt just below the costal margin on the right. This mass was not tender and was very smooth. There were no abnormalities of the rest of the abdomen. Pelvic examination was not remarkable. The urine was not abnormal. The hemoglobin was 11 grams; red blood count 4,190,000; leukocyte count 7,600; differential normal; Wassermann negative.

The patient was admitted to the hospital on May 19, 1941, for studies, after persistence of symptoms. Biliary drainage at this time showed normal bile. Cholecystograms revealed non-filling of the gall bladder. Hippuric acid test was .42 mg., cephalin cholesterol test was +2, icteric index was 6.2. Stool examination was negative. Basal metabolic rate was —20 per cent. The patient was discharged on May 29, 1941. The impression at this time was that the patient had gallbladder disease with cirrhosis of the liver.

She was followed in the outpatient department following this admission. The abdominal pain persisted. Cholecystograms were repeated and showed normal filling of the gall bladder. The mass in the right upper quadrant continued to enlarge.

The patient was brought into the hospital again on December 1, 1941. At this time the liver function had returned to normal. Pyelograms were made and showed the left kidney in normal position; pelvis and

calices normal. The right kidney was shown to be displaced to the left of the midline with evidence of rotation so that many of the calices were directed to the left side of the spine. A very large tumor shadow could also be made out in the right upper quadrant. Previous to the cystoscopic examination our impression had been that the abdominal tumor had nothing to do with the kidney, but after seeing the pyelogram a diagnosis of retroperitoneal tumor, possibly of right kidney origin, was made (Fig. 1). Indigo carmine was excreted in good concentrate in four and one-half minutes on the left and five minutes on the right. Urine from each kidney showed rare leukocytes.

On December 6, 1941, operation was done. Through a subcostal incision on the right the abdomen was entered. A large cyst was found running down to the head of the pancreas. The cyst was whitish in color, very thick walled, and covered with large dilated veins. The right kidney was palpated, and was entirely separated from the cyst and had been pushed down and to the left of the vertebral column. The cyst was opened and two liters of mushy black material removed. The material had a high content of greasy substance and what appeared to be old blood and degenerated tissue. After removing this material the cyst was marsupialized. The diastatic content of the cyst material was 15 units. Blood diastase was 23.7 following operation. Culture of the cyst revealed hemolytic streptococcus. Convalescence was uneventful and the patient was discharged sixteen days postoperative. About a month later pyelograms were made again and showed the right kidney had migrated back to the right of the midline and up towards the normal position. Slight hydronephrosis was present (Fig. 2). Drainage from the cyst gradually ceased and ten days following operation the cyst held only 15 c.c. Sclerosing solutions such as sodium morrhuate were introduced at frequent intervals. Eleven weeks after operation drainage had almost entirely ceased.

Remarks.—The differential diagnosis in this case presented a difficult problem. There was no history of trauma, nor was there anything in the history which could be construed as an attack of acute pancreatitis, which would have given some evidence in favor of a pancreatic cyst. The pyelograms gave evidence supporting the theory that the tumor had originated in the right kidney or above and lateral to it. Because cyst appeared anteriorly and could not be easily palpated in the flank, the subcostal incision for exploration was used. The cyst in this case arose from the head of the pancreas and must have been originally below the level of the upper pole of a normally placed kidney. It may have been a ptotic kidney or an ectopic kidney. It is difficult to determine from the pyelograms, and at operation we could not be certain. Our impression is that it was probably a ptotic kidney. Be this as it may, the cyst in its expansion extended into the right renal fossa, although it never

filled it completely, and pushed the kidney downward and medially until it lay to the left of the midline. This represents an unusual presentation for a pancreatic cyst. While the point of presentation is influenced by the point of origin, the pancreatic cyst most commonly pushes directly forward through the floor of the lesser sac, carrying the stomach forward with it, and as it becomes larger pushes between the stomach and colon. A second form of presentation is that in which the cyst passes forward around the stomach to the anterior abdominal wall. A third form of appearance of the cyst anteriorly is that where the cyst pushes forward between the layers of the transverse mesocolon and then may bulge up toward the stomach or down toward below the colon. In the type of cyst discussed in the case reported here, where the cyst had its origin in the retroperitoneal collection of the products of inflammation in the pancreas, the presentation might naturally be more irregular than in the true cysts. Apparently here the products of breakdown of the pancreas had gravitated into the right renal fossa and then, as the cyst formed, pushed the kidney down and medially, at the same time pushing directly forward to touch the parietes just under the costal margin below the liver.

As to the treatment in this case, marsupialization and the use of sclerosing solutions was decided upon due to the dangers of attempting the removal of a pancreatic cyst in this location.

Case 2.—J. O., was a thirty-seven-year-old Irish shipping clerk who was admitted to the Henry Ford Hospital on the Medical Service on November 9, 1941. His chief complaints were: (1) vomiting of eight to ten days' duration; (2) pain in the left upper abdomen of two days' duration; (3) pain in the left lower chest radiating to the tip of the left shoulder of two days' duration.

The present illness was preceded by a drinking spree of fourteen days prior to hospitalization. After four days of heavy drinking the patient was said to be "very drunk and very nervous." He was placed in a convalescent home. He vomited for the next six or seven days, when, as this gradually subsided and he was just beginning to "feel like himself again," he developed acute pain in the left side of the abdomen (forty-eight hours before admission). This pain was fairly sharp and constant, although crampy at times. It was severe enough to keep him awake. It radiated upward through the left chest to the tip of the left shoulder and was made worse by deep breathing. The pain was followed by a fever but no chill. A slight cough associated with brownish sputum developed and there was shortness of breath. The nausea and vomiting returned and became very persistent. The bowels did not move for two days and the patient complained of much gas. He had a mild dysuria and frequency.

The past history showed chronic alcoholism with recent excesses. In the past two years there had been several periods of intoxication, often followed by nausea and vomiting, and in the past year there had been three attacks of dull aching pain in the left upper quadrant of the abdomen and in the epigastrium. This pain was similar to the abdominal pain which he associated with the present illness, although it had never been as severe and there had never been an associated pain in the chest or shoulder. There was no history of jaundice, constipation, diarrhea or melena, or of previous urinary tract symptoms. No history of tuberculosis, diabetes, typhoid or pleurisy could be elicited.

Examination on admission revealed a well developed, moderately obese, acutely ill white male whose temperature was 102, pulse rate 130, and respirations 48. He appeared dyspneic but not cyanotic, and there was no dilatation of the ala nasi. The throat was moderately inflamed. The thyroid was not enlarged. The cervical lymph nodes showed no abnormality. The chest movements were limited, the diaphragm remaining high on both sides, with possibly a little more limitation of motion of the left. The percussion note was impaired over the left lower lung field posteriorly. There were many moist râles and tubular breath sounds in this area. The heart was not enlarged to percussion, and the rate was rhythmical and regular and no murmurs were heard. Blood pressure was 110/80. The vessel walls showed no evidence of thickening. There was tenderness to fist percussion over the left costovertebral angle. The abdomen was distended and very tense and had generalized tenderness. There was splinting of the left rectus muscle. The greatest tenderness was present in the left upper quadrant and rebound tenderness was present here. No abdominal masses could be felt. The external genitalia were not abnormal. Rectal examination showed nothing unusual. There was no rigidity of the neck or spine. The extremities were not abnormal.

The initial laboratory work revealed hemoglobin 13.5 grams per 100 c.c. blood, red blood count 4,480,000, white blood count 7,650, with 85 per cent polymorphonuclears. The white count a few hours later rose to 12,350. Urinalysis showed specific gravity 1.029, acid reaction, albumin 0, sugar 2 plus, acetone and diacetic acid 0, and bile 0. Microscopically there were a few white cells, a few hyaline casts and a few finely granular casts. The stool was tarry in appearance, of semi-liquid consistency, and showed a 3 plus guaiac. Sputum was typed and showed pneumococcus Type 16 with organisms being very numerous. Blood sugar showed 382 mgm. per cent and CO_2 combining power was 25.3.

The patient was started on sulfadiazine and he tolerated this drug very satisfactorily. The dullness in the left chest remained unchanged for three to four days, after which it decreased. The left diaphragm, however, remained high, and the tenderness in the left flank persisted. The patient continued to have distress in the left upper abdomen and the abdominal distention persisted, associated with nausea and vomiting.

A blood diastase determination five days after hospital admission

showed 14.3 mgm. per cent. The white blood count ranged between 12,000 and 15,000 for the first week and then it rose to 21,000. On one occasion microscopic blood was found in the urine.

Five days after hospital admission a mass could be felt on bimanual palpation in the left flank. The temperature had ranged from 100 to 103 degrees since the day of admission. Three days later pyelograms were made which showed no displacement of kidneys.

A diagnosis of perinephric abscess was made and plans were made to incise and drain it. On November 24, ten days after a mass was first noted, the patient was taken to the operating room, but under the preanesthetic medication examination of the abdomen revealed a second mass in the upper abdomen just left of the midline.

An x-ray of the barium-filled stomach revealed a large elliptical-shaped deformity in the greater curvature produced by the anterior abdominal tumor mass. Two days later incision and drainage of the mass in the left flank through the usual kidney incision was done and a fairly thick-walled cyst was found which contained approximately 400 c.c. of a dark red fluid. This was in immediate proximity to the lower pole of the left kidney, but careful examination of the kidney showed no break through the capsule. A cigarette drain was inserted and this incision was closed. The patient was then placed on his back and the anterior mass was found to be unchanged, showing that it was not connected to the flank mass. A second incision was made in the midline of the upper abdomen and a large cyst was found filling the lesser peritoneal cavity; this contained about 800 c.c. of dark red fluid identical with that drained from the cyst in the kidney region. Considerable bleeding followed the drainage of this second cyst and it was necessary to pack it with gauze to control the hemorrhage. The wall of this cyst was marsupialized.

A diastase determination of the fluid drained from the cyst was 62 mgm. per cent. A blood diastase determination the day following incision and drainage showed 38.9 per cent.

The convalescence of this patient was slow but entirely satisfactory. He was discharged from the hospital nine weeks after operation, the left flank incision wound having healed entirely. The epigastric incision wound was still draining and it continued to drain for three weeks longer. Since then there has been no evidence of any further inflammatory process or recurrence of a cyst. The patient has a mild diabetes which has been easily controlled by diet and small doses of insulin.

Remarks.—In this case the diagnosis of pneumonia was not difficult, but this made the remaining symptoms more confusing. The formation of a pseudocyst of the pancreas undoubtedly followed upon an attack of acute pancreatitis. The products of the inflammation and degeneration of the pancreas gravitated to the left loin and burrowing through the fat about the kidney emanated upon the parietes below the border of the last rib. The gravitation of

this material took place retroperitoneally. The mass appearing in the left flank with costovertebral tenderness, slight edema of the subcutaneous tissues, fever, leukocytosis, and microscopic hematuria, gave definite signs which pointed to renal or perirenal disease, the most likely diagnosis being a perinephric abscess, and only after the development of a second mass which presented in the most common place for cysts of the pancreas, was this second diagnosis suspected.

Case 3.—F. G., a white man of forty, underwent operation on August 25, 1937, for pancreatic cyst. At the time of operation the cyst was found to originate in the tail of the pancreas and was marsupialized. Drainage continued for three months. On February 22, 1938, he was again admitted to the hospital with pain in the left flank of three weeks' duration and radiating down across the abdomen into the testicles. The pain was of sufficient severity to double the patient up. There were no associated digestive disorders nor any genito-urinary symptoms. Pyelograms showed no abnormality in the kidney, but it was not until a second marsupialization of the cyst was carried out that it was certain the kidney was not involved.

Remarks.—This case is only briefly reviewed because the first operation made the diagnosis clear. It is presented to emphasize the fact that typical renal-ureteral distribution of pain originated in a pancreatic cyst. This was probably due to pressure on the left kidney by the cyst.

In addition to these three instances of confusion of diagnosis which have come under our observation we have found six other cases reported in the more recent literature and are giving herewith brief abstracts of them.

1. Trattner and Galvin (1940) reported a case of acute pancreatitis which simulated a case of perinephritic abscess. In their case the mechanics of the process seem to have been identical with those of Case 2. Early operation was performed in their case with a fatal outcome.

2. Johnson reported a case of pancreatic cyst appearing in the left flank and simulating left hydronephrosis.

3. Ferguson (1936) reported a case of infection passing to the pancreas from a perirenal infection and causing a peripancreatitis and comments that, although there is close proximity, no previous instance of peripancreatitis of this origin had been reported.

4. Ransohoff reported a case of pancreatic cyst accompanied by unilateral hematuria. The patient was a man of sixty-one years

with a large tumor of the left upper quadrant and blood in his urine which was found to be coming from the left ureter. There was no pyelogram, but a diagnosis of malignant tumor of the left kidney was made. Operation disclosed an apparently normal left kidney and a large retroperitoneal cyst. No explanation of the hematuria was found.

5. Walters and Thiessen report a case of sebaceous cyst of the pancreas felt as a large fixed mass in the left upper quadrant. Pyelogram showed elongation of the upper calyx on the left and exploration was done through a kidney incision. The kidney was found to be normal. The peritoneum was opened and a cyst found in the tail of the pancreas from which 1500 c.c. of milky, flaky fluid was obtained. The pathologic report of the cyst wall was sebaceous cyst.

6. Kummer reported a case of a large pancreatic cyst in a woman aged thirty-one, obliterating the calyces in both intravenous and retrograde pyelograms of the left kidney and leading to a diagnosis of kidney tumor.

SUMMARY

Three cases are reported in which there was a differential diagnostic problem between pancreatic cysts and some urologic condition. In addition, six somewhat similar cases in the literature are cited.

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DISCUSSION

DR. LEON HERMAN (Philadelphia, Pa.): I should like to say a word about polycystic kidney. Until rather recently, I thought the diagnosis of polycystic disease was a rather simple matter. During the last year we have had three operated non-diagnosed cases, which have rather changed my opinion. Two of these patients were Negroes, one an old lady, the other a man of about thirty-five. Both of them had large tender masses on one side; pyelograms of the other side showed a normal condition. We thought they were very clear-cut cases of pyonephrosis, but exploration showed polycystic kidney in each instance. The disease is bilateral undoubtedly, but of the apparently non-involved side the defect had not progressed to the point where it was demonstrable.

The third case was a woman of sixty-five who came to us two years ago with hematuria. We discovered that she had a congenital single kidney. It was a large kidney. There was no ureter on the opposite side and the trigone here was undeveloped. I didn't do a pyelograph because I feared to do so, but we made a secretory urogram which showed a defect that suggested a neoplasm. I thought her fate was sealed. She went home and I had forgotten all about her when more than two years later her doctor called me up and said she had had a sudden severe pain in the right loin three days before, which was followed by hematuria and anuria. She was semicomatose when brought to the hospital and was able to distinguish light but nothing else. I catheterized her ureter with ease, drained off some heavily concentrated, retained urine, and her renal function was slowly restored. After about two weeks of catheter drainage we got her blood chemistry down from 70 mgm. of urea to normal, then did a retrograde pyelogram. Her kidney was displaced outward. It was rotated so the medial border was pointing forward partially. The stereoscopic study showed the ureter projected forward and the deformity did not suggest polycystic disease. It had the usual features of back-pressure.

We deemed it justifiable to explore the loin, which we did, and found a cyst about as big as a walnut on the convex border slightly anteriorly, together with four or five smaller cysts, and at the lower pole of the kidney there was a cyst about the size of a large orange.

This was a cyst into which a sudden hemorrhage had occurred, pushing the ureter forward and kinking it; this was the obvious cause of her difficulty. We opened the cyst and, fearing we might precipitate a hemorrhage, removed only part of the blood clot, put a drain in and the patient had an uneventful recovery. She is entirely well at the moment.

These cases illustrate insurmountable difficulties in the diagnosis of complicated polycystic disease of the kidneys.

DR. WILLIAM P. HERBST, JR. (Washington, D. C.): I would like to comment on bichloride anuria which Dr. Hamer mentioned and covered so thoroughly. I have had four cases of bichloride anuria. I operated on three of these patients, none of whom recovered. The one patient who did not wish to be operated on and on whom I didn't urge operation, after having been anuric twelve days, got well by himself.

I would like to know what Dr. Hamer thinks about the advisability or inadvisability of decapsulating in these toxic anurias.

DR. EDWIN DAVIS (Omaha, Nebr.): Referring to Dr. Hamer's paper, I wonder whether transfusion of properly matched blood, as a cause of complete urinary supression, terminating fatally, has come to the attention of members of this audience. I have recently seen one such patient in consultation with a dependable internist who reported to me having seen three others, all terminating fatally.

DR. GEORGE R. LIVERMORE (Memphis, Tenn.): In regard to anuria following bichloride of mercury poisoning, you will remember our lamented friend, Harry Sanford, reported before this Association three cases some years ago, in which decapsulation was done with recovery of all three. I have seen a number of such cases and I reported before this Association some time back a case of lysol poisoning in which decapsulation was done, with nephrostomy, and the patient recovered. I think that it is an operation that should not be denied the patient when all other measures have failed, despite the fact of Bill Herbst's report on the case that got well under non-operative procedures after he discussed decapsulation. I think nephrostomy adds to decapsulation, and I believe it should be done in these cases.

Also, in that type of case which results from postcystoscopic

trauma, a reflex anuria from cystoscopy, it has been my observation that such patients usually recover without any difficulty, if the kidney function is fairly good. If the kidney is badly damaged, many of these cases may go on to complete uremia and death.

DR. LEON HERMAN (Philadelphia, Pa.): I was reminded last night of a patient with arsenical anuria by Dr. Colston. Dr. Colston now has my patient and despite years of friendship and despite all my suggestions, I am inclined to believe he is going to keep him. (*Laughter*)

This patient was given 3 decigrams of neosalvarsan by the late Dr. Thomas Stelwaggen. He developed anuria immediately. He was in the Jefferson Hospital and had been there two days. A medical consultant had given him some mercury intravenously, which I don't imagine helped any. On the third day I saw this man. Dr. Stelwaggen had had an attack of angina that afternoon. The next night, the fourth night, Dr. Stelwaggen died, and at midnight Dr. Kinney and I decapsulated the kidneys of the very sick patient.

No urine was excreted during the next twelve hours and then function returned and enormous quantities of urine were voided. Forty-eight hours later an enormous duodenal hemorrhage from an ulcer occurred. We gave the patient continuous glucose for a ten-day period and transfusions numerous times, and he left the Jefferson Hospital with normal blood urea, normal phenolsulphonephthalein, and nothing except a trace of albumin in his urine.

Dr. Colston told me last night that this patient appeared at his clinic some time ago, still with normal kidney function, but that he now has developed a couple of small stones in one of his kidneys, I think the right one. This patient recovered from decapsulation but I have had no recoveries in cases of mercury poisoning. We had a recovery from mercury poisoning in a girl after five days of anuria without any surgical intervention. In all my mercurial cases that have been decapsulated, the patient died.

DR. J. C. MCCLELLAND (Toronto, Canada): I enjoyed Dr. Hamer's paper very much. There is one group of patients I think we should mention today, since this is a time of war. This is the group of crush injuries. In England, at the present time, a great many people who are being crushed under the bricks and mortar and stone

buildings that are being knocked down due to the bombing, develop quite an area of contusion in the muscles, along with some fractures. These areas of contusion are said to give off some sort of a toxin that within twelve hours would produce anuria. This anuria is complete. The patient will be fairly well for a period of six or seven days and then will die suddenly. During that time, there are the usual signs of anuria, where the non-protein nitrogen increases, a little bit of edema comes on, and then suddenly on the sixth or seventh day the patient dies.

When autopsies are performed, nothing very much is found except the signs of an acute nephrosis in the kidney, the signs of absorption of toxin.

We have observed similar types of patients in our Northern Ontario mines. I had the privilege of seeing one of these two years ago. This man was under a rock fall, where he had a good deal of contusion of his whole left thigh, left side of his back, his left chest, and some hemorrhage into the left lung. He developed anuria. He went through this same series of symptoms as these crush injuries do in England at the present time, and he died twenty-four hours after complete bilateral decapsulation. When his kidneys were exposed, they showed a rather pale, white color and were under considerable tension. On removing the capsule, the kidney seemed to soften up a little. Within the next twelve hours he passed two or three ounces of urine which was blood stained, contained a few casts and a large quantity of albumin.

When he died, we had an autopsy. He had this picture which I have mentioned, contusion of the muscles, and the microscopic sections of the kidneys showed nephrosis.

Transfusion has been used as treatment for these people and it hasn't benefited them. They have also received the different types of intravenous therapy which is being used now for shock, and that hasn't helped, but some of them have got some intravenous soda bicarbonate in fairly large quantities, which seems to help.

We didn't use sodium bicarbonate on our patient. The only thing we did use was intravenous fluid plus the bilateral decapsulation. These cases are occurring more frequently now and if any bombings should come to this continent, no doubt we will see some of these cases.

DR. ALEXANDER RANDALL (Philadelphia, Pa.): Dr. Hamer,

we are greatly indebted to you for your exposition of anuria. It might be of interest to you that some twenty-odd years ago, a group of us trying to make one of these things called a symposium chose the subject of anuria and we searched around the country trying to think who would best present the subject. We started the idea of prerenal, renal and postrenal anuria. We had chosen Hugh Cabot to take the most difficult proposition, that is, the prerenal anuria. I can well remember a letter which came from Hugh, quite characteristic, "What in the hell is prerenal anuria?"

Well, it was interesting, therefore, to find in the last edition of his own book, in which he was handling the subject himself, that he had adopted this classification, and it is the one which Dr. Hamer has used today. It unquestionably classifies your own individual cases into definite types, in each of which treatment varies.

No one worries about the postrenal anurias. One simply removes or sidetracks an obstruction. Dr. Hamer has mentioned some of the prerenal anurias, but he has omitted, as I heard him, speaking of those in which blood pressure plays a part. We have seen them in a number of clinical conditions and I think they are part of Dr. Vincent O'Conor's report on the anuric state which comes with the decompression of an overdistended and chronically obstructed bladder.

Now, in regard to the true renal anurias, by this classification one ought to be able to get to a very rational, prompt approach to the problem. They are acute surgical conditions and you must strive in the proper direction if you are going to save the patient.

A number of comments have been made in regard to the bichloride anurics. We were fortunate in working with Leonard Rowntree in our cases and I think he had a little more logical reasoning as to what you have and what you ought to do. What does bichloride do? It creates an intense chemical destruction of the cells lining the renal tubules. It apparently rarely involves the glomeruli. The picture just mentioned of the tense kidney in shock from crush injury is probably very close to the same story. It is also probably the same picture that is seen with any acute intoxication with anuria. Very close to it, too, will be the acute infectious anuric condition, all due to tubular damage and tubular blockage.

It is hard for one to foretell, but the number of cases on one side of the room which recovered from decapsulation and the ones on the other side of the room that didn't, don't mean anything. De-

capsulation is a proper thing to do simply to relieve capsular tension and in so doing enable a kidney to excrete its glomerular fluid down its individual tubule.

Now, there are two things of interest if you examine closely—I mean not only microscopically but chemically. The first is that the urine put out by such an anuric kidney, the first urine, is washing debris out of the tubules. The clinician is apt to sit back and say, "Fine, I have broken his anuria. He is now putting out so many ounces of urine."

But examine that urine and you will find it is nothing at all but glomerular fluid, and from that moment on, in those who are to recover, the tubule lining cells are slowly but actively regenerating to reform a lining membrane, instead of a sheer tubule. It is not yet ready to pick up tubular renal function, and during that interval the patient is a great deal sicker than he was when he was anuric, because he is simply washing out through his renal system vital metabolites, vital salts, and unless you control it, he will die of his own renal activity or lack of retention and lack of resabsorption. It will be noticed that his blood urea nitrogen, his blood creatinine, et cetera, will continue to go up and he will lose chloride, sugar, et cetera. That is the one point where you want an active, interested and ceaselessly working laboratory. Then you must watch the patient's blood and you also must watch the urine output and its character.

One man reports the advantage of giving bicarbonate, another man reports the advantage of doing this and doing that, but to be intelligent you must closely watch the patient's chemical balance and replace what he is innocently losing; he is always sicker for the next three, four or five days following the cessation of the anuric state, while the regeneration of tubular cells progresses and a return to normal tubular absorption and function is once again gained.

Dr. Clarence R. O'Crowley (Newark, N. J.): Within the past year, I had under my care at one of the hospitals two men in their thirties. They had been subjected to the fumes of carbon tetrachloride from cleaning preparations. They were brought into the hospital anuric. After watching them a little while, about the usual study, they had the same pictures that all these chemical cases have. One allowed a double decapsulation and the other fellow re-

fused. The one with the decapsulation died in three days; the other one died in three weeks. But he established urinary output, plenty of urine with an absolute to zero specific gravity during that time. So we thought we had the problem settled at that time, that one could get along without it and the other had to have it; but they both died.

Dr. Thomas P. Shupe (Cleveland, Ohio): Recently, in fact last week, a case was reported in Cleveland by Dr. Trattner from City Hospital. The treatment of this case may give some clue as to the handling of these actue nephritis cases from toxic material, from whatever cause, either bichloride or toxic material from contusion. This was the case of a man with bichloride poisoning. Just how much bichloride the individual had absorbed, we couldn't tell because he had vomited, but his blood urea and nitrogen were very high and the creatinine, the same way. He was treated by multiple transfusions, two a day, with bleeding each time. That is, about 200 c.c. of blood were removed and about 400 put in. That was done, as I said, twice a day. He was given soda bicarbonate intravenously. One kidney was decapsulated; one kidney was left alone. The patient recovered. Postoperative retrograde pyelograms were made and showed the kidney that was decapsulated in much better functioning condition as to the appearance of the pyelogram and the output of indigo carmine than the kidney that had not been decapsulated.

Dr. Howard Jeck (New York, N. Y.): About fifteen years or more ago, I attended a Bellevue Alumni meeting in New York, at which Dr. John Rogers, the thyroid man, was the chief speaker. He said in his experimental work on dogs he had noticed that thyroid residue, one of the substances he was using, was a great kidney stimulator. He said, "I would advise some of you urologists to try this in cases of anuria," presumably of the excretory type. It just so happened that about two days after that, a patient was admitted to the urological service at Bellevue with a single kidney. He had been in anuria for about five days when he came in. We procured some of this thyroid residue, gave it to him according to Dr. Rogers' instructions and within twelve hours, he was putting out large quantities of urine.

Now, of course, that doesn't necessarily mean anything because this man had gotten intravenous fluids and what have you, up to

that time; but it rather encouraged us and we have given it in a fairly large number of anuric cases since then, both in Bellevue and elsewhere, and many of these patients have rather promptly come out of their anuria.

The preparation that we use is called Thyroid Residue, put up in sterile ampouls, by Schiefflein & Company, of New York. It is the only place you can get it that I know of. The dosage is 20 to 30 minims intramuscularly about every two hours for some six or eight doses. If results are not obtained by that time, the continuation of the drug is probably not advisable.

DR. C. D. CREEVY (Minneapolis, Minn.): May I have just one moment to say that I still know of no acceptable evidence to the effect that sudden emptying of a chronically distended bladder will of itself cause anuria or any other untoward reaction.

DR. HERMON C. BUMPUS, JR. (Pasadena, Cal.): I should like to ask Dr. Randall a question. Clinically the urine of these cases has a very low specific gravity, as Dr. O'Crowley said. If these patients are losing a lot of their salts, why doesn't the specific gravity rise? Isn't it the retention of toxic substances that they are not getting out that makes them so dangerously ill when they start to secrete, rather than the fact they are losing salts? If they were losing salts in the urine, then the specific gravity ought to go up and not remain near that of water.

DR. RANDALL: Not if you think of it only as glomerular fluid which is nothing more than blood serum without protein.

DR. HOMER G. HAMER (Indianapolis, Ind.): The many queries that were addressed to me in discussion have been largely answered by the discussants themselves.

In the study of anuria, I had a good deal the feeling that Dr. Randall had when he read his paper on anuria before the American Urological Association several years ago. I, too, was looking for the true case of reflex anuria, and while such may occur, convincing proof is lacking. Dr. Irvin Page told me recently of some experimental work on emotional excitation in stimulating diuresis and oliguria, but it is not ready for publication. Doubtless there will be something on that line before many years.

URETERITIS CYSTICA WITH HEMATURIA

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As early as 1761 Morgagni[7] described ureteritis cystica in this concise manner:

"In the mucous membrane of the urinary tract, especially of either ureter, generally in large numbers and groups, there sometimes arise cysts varying in size from that of a grain of wheat to that of a pea, and others of microscopical dimensions. They contain a thin serous or thick colloid, clear or yellowish brown fluid, or gluey resinous clumps."

Von Brunn,[11] in 1893, described epithelial bodies lying below the mucous membrane of the urinary tract showing an epithelial connection with the surface epithelium. These he designated as epithelial buds or sprouts and those bodies showing no such epithelial connection he called epithelial nests. He was not able to find glandular elements in the wall of the ureter and thought that cyst formation was due to degeneration of the central cells of the nests as part of an inflammation. Giani was able to produce experimentally these formations in the bladders of laboratory animals by introducing chronic inflammation.

In 1927 Morse[8] made a careful microscopic study of the kidneys, ureters, and bladder in 125 consecutive necropsies. His conclusions were that glandular structures are not present in the ureter or kidney pelvis. He found the epithelium inclusions of Von Brunn in 86 per cent and in over 50 per cent lymphocytic infiltration or fibrous tissue proliferation was present. He states that microscopically epithelial buds, cell nests, and cysts are present in the majority of persons over twenty years of age. Crypts of mucous membrane may occasionally become closed off by proliferation of fibrous tissue; these crypts Morse thinks may mistakenly be called cysts.

In 1929 Joelson[5] first demonstrated ureteritis cystica in pyelograms.

Patch,[9] in 1935, stated that the mucous membrane of the urinary bladder when exposed to chronic inflammation may undergo metaplastic changes which may result in leukoplakia, formation of the cell nests of Von Brunn, cystitis cystica and cystitis glandularis.

He also thought these lesions were potentially precancerous (in which view Hinman, I believe, concurs) but admitted that the details of the progressive changes were lacking. In his report Patch used material from twelve cases, eight of which were obtained by operation and four by necropsy. In two of these cases clinical observation would seem to show that the disease can disappear and in two other cases chronic inflammation as a cause was not apparent.

It seems well established now, however, that ureteritis cystica is a pathologic entity related to infection and chronic inflammation.

The condition is usually asymptomatic and attention is not drawn to the urinary tract. The majority of reported cases have been recognized at necropsy and often were wholly unexpected findings. The condition is much more common than reports in the literature would seem to indicate. Many early cases are undoubtedly overlooked in pyelograms, or the filling defects attributed to "air bubbles." The lesions are bilateral, though the cysts may be more numerous on one side than the other.

The chief effort in therapy is directed towards freeing the urinary tract of infection. Kindall[6] suggests the use of a large indwelling catheter, thereby hoping to rupture the cysts. On removal of the catheter he advises an injection of 2 per cent solution of silver nitrate into the renal pelvis with the idea of destroying other cysts. Appended to Kindall's article is a most comprehensive list of references for anyone caring to review this subject. The use of deep x-ray therapy has been tried, but no one type of therapy has been successful.

During the last year we have had two patients with ureteritis cystica, diagnosed clinically, one occurring with horseshoe kidney. Both patients were admitted to the hospital with hematuria, one patient requiring repeated transfusions. In both patients the hematuria followed trivial injuries. Hypertension was present in one patient. Both of these patients had staphylococcal infections of the upper urinary tract.

Case 1.—The patient, white, male, aged fifty-four, was admitted with slight soreness in the left lumbar region and hematuria of two days' duration following slight trauma. Blood pressure was 150/90. Blood picture and non-protein nitrogen were normal. Serology was negative. Cystoscopy showed several small cysts in the region of both ureteral

orifices. Pyelogram showed ureteral cysts of both ureters, kidneys functioning actively. Urine culture was Staphylococcus aureus.

The pyelograms of this patient have been observed over a period of a year without any change, although clinically the patient is well and working hard as a mechanic daily. The infection is not severe, but is still present after a year, in spite of sulfa drugs and other therapy.

Case 2.—The patient, white, male, aged fifty-one, was admitted because of slight pain in the left lumbar region and hematuria of two

Fig. 1. *(left)* Case 2. Ureteritis cystica. No change in pyelograms after a year of therapy. (The left pyelogram showed the condition better than the right side.)

Fig. 2. *(right)* Case 2. Ureteritis cystica with horseshoe kidney. Hematuria was marked in this patient.

weeks' duration. Bright red blood appeared with every urination. Blood pressure was 180/110; hemoglobin 70 per cent; hematocrit 40 per cent, non-protein nitrogen normal, serology negative, no fever.

Cystoscopy showed several small and large cysts distributed throughout the bladder singly and in clusters. The bladder mucous membrane was congested. There was moderate enlargement of the prostate gland (benign). Pyelograms showed ureteritis cystica on both sides occurring with a horseshoe kidney, both sides actively functioning, moderate hydronephrosis left. Staphylococcus aureus was found in the urine.

In this patient, whose hemoglobin fell to around 45 per cent, repeated small transfusions were given. Varying strengths of silver ni-

trate solutions were used in the kidney pelvis and deep x-ray therapy was tried. The patient stopped bleeding entirely in about two months. Infection, however, persists, also in spite of sulfa drug therapy. Repeated pyelograms show no change in position or character of cysts. Clinically the patient is weak and unable to resume his manual labor.

A brief summary of ureteritis cystica is presented indicating the underlying chronic inflammatory nature of the disease.

Two cases are presented, both diagnosed clinically as having ureteritis cystica. Both patients had bilateral renal hematuria on admission, one moderate and one severe. Mild, chronic infection (staphylococcal) was present in both patients. Both had the sulfa drugs intensively but without a complete cure in either patient. In one patient ureteritis cystica occurred in horseshoe kidney. One patient had mild hypertension. In one patient, who has been symptom-free for a year, the pyelogram is unchanged.

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THE EFFECT OF IRRADIATION ON THE LOWER URETERS

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Ureteral obstruction complicating cancer of the cervix is well recognized. Behney[1] found this to be the cause of death in 21 per cent of 166 women with cervical cancer; in 65 per cent of the entire group the ureters were found to be dilated. In a series of more than 100 patients, Howes and Strauss[6] found ureterorenal pathologic lesions on the right side in 23 per cent, on the left side in 10 per cent, and bilateral in 19 per cent.

These investigators attribute the ureterorenal disease to one of four factors.

1. Ureteral blockage due to inflammatory parametritis.
2. Involvement of the ureteral wall and sheath by carcinoma.
3. Ureteral obstruction, in a small number of cases, due to transient edema following irradiation.
4. Ureteral obstruction due to post-irradiation fibrosis. The same authors state that the site of obstruction is usually from 4 to 6 centimeters above the ureterovesical junction, at the point within the broad ligament where the ureter lies nearest the cervix.

Our interest in this condition was aroused by the problems presented in a small series of patients upon whom we had operated. Three had unilateral ureterostomies. One had bilateral nephrostomy; the fifth should have had nephrostomy. Although this series of five patients does not compare with the large series reported by Graves, Kickham and Nathanson,[5] we found several points of interest which appear to warrant discussion. These points include the pathologic condition underlying the obstruction, the etiology of the pathologic condition and the question whether the obstruction is temporary or permanent.

Case 1.—A woman aged forty-nine was first treated in 1932 for epidermoid carcinoma, grade II, of the cervix. In April of that year she was given 4240 millicurie hours irradiation by means of a silver cylinder placed in the cervico-uterine canal and by eight gold seeds

of 1.5 mc. each implanted in the wall of the cervix. In August, 1933, a lead bomb placed in the crater of the cervix yielded 2200 mc. hours. The ureteral obstruction was not discovered until six years later. At that time the right ureter was completely occluded and could not be catheterized. The left ureter was catheterized several times, but com-

Fig. 1. Case 1. Low power photomicrograph of section of lower ureter showing fibrosis but no cancer.

plete anuria then required a ureterostomy. This was carried out on March 13, 1939.

The pathologic condition consisted of a rather gradual narrowing of the ureter, the change from a diameter of 1 centimeter to one of 2 millimeters occurring within a distance of from 2 to 3 centimeters.

At the point of smallest diameter the ureter was very friable and broke away as it was being freed. The terminal centimeter of this upper segment was removed for pathologic examination.

Sections of this ureter showed "fibrous and muscular tissue with slight chronic inflammation" (Fig. 1).

Fig. 2. Case 2. Urogram showing stenosis of lower left ureter.

From that time on the patient was never very well. She had an extensive abscess in the pelvis which was incised and drained several times without ever being thoroughly cleared up. In August, 1940, she ran a persistent fever which was believed to be due to a closed pyonephrosis of the right kidney. The right kidney was removed but proved to be a sterile hydronephrotic sac. On December 24, 1940, the patient died at home; there was no autopsy.

Case 2.—A woman of fifty-three with an epidermoid carcinoma, grade II, of the cervix, was treated in October, 1935, by means of gold seeds implanted in the periphery of the cervix and a silver capsule

containing radium element in the cervico-uterine canal. The total dosage was 4344 millicurie hours. In November, 1937, she developed incontinence of urine and dysuria; her non-protein nitrogen was 52 mg. per cent. Cystoscopy showed nothing remarkable in the bladder. The right ureter could not be catheterized for more than 2.5 cm. The left ureter was catheterized and a urogram (Fig. 2) showed marked dilatation of the ureter and pelvis (Fig. 2). A No. 9 French catheter was left in the ureter for three days with marked relief of the patient's symptoms, and on December 31, 1937, a left ureterostomy was done through a left oblique lumbar incision. The ureter was divided at the level of the iliac vessels and the site of actual obstruction was not investigated.

The pelvic induration continued to increase and the patient died on November 14, 1938, three years after her initial treatment. Autopsy showed extensive carcinomatosis, with radium reaction in the colon, uterus and cervix. The right kidney weighed only 50 grams. The right ureter was completely obstructed by fibrous tissue contraction below the pelvic brim. The left kidney weighed 120 grams and showed atrophy and pyelonephritis.

Case 3.—This case was similar in etiology and in general features to the preceding two. Seventeen months after an irradiation of 3,993 millicurie hours, the patient developed bilateral obstruction. The right ureter was completely obstructed, and at operation the left ureter was found to be spindle-shaped and to taper down to a thin strand which broke away as the ureter was being freed. A portion of the ureter was removed for examination and showed "almost complete obliteration of the lumen which is lined in part by stratified, slightly keratinized epithelium, in part by fibrin, lymphocytes and connective tissue. Muscle content and submucosa infiltrated by clusters and strands of rather small tumor cells showing frequent mitoses." This latter description agrees with that of two similar cases reported by Bugbee,[2] in that both tumor cells and fibrotic reaction were present.

The patient died at home and no autopsy was obtained.

Case 4.—In September, 1937, a woman of fifty-one with cancer of the cervix was given 4,144 millicurie hours irradiation by means of gold seeds and a silver capsule containing the radium element. Something over three years later, in February, 1940, cystoscopy showed, just above the trigone, a raised, ulcerated area surrounded by edematous mucosa and covered with slough. The appearance of this lesion, although suggestive of a radium ulcer, had some of the characteristics of malignant infiltration. Two biopsies were made at different times; both showed only chronic inflammation. The intravenous pyelogram was normal; the non-protein nitrogen was 31 mg. per cent.

On May 21, 1940, intravenous pyelography showed moderate bilateral hydronephrosis and hydro-ureter. The non-protein nitrogen

was 36 mg. per cent (Fig. 3). Bilateral nephrostomy was done by one of us (W. L.). Three months later the nephrostomy tubes became displaced and ceased to drain, but the patient was voiding freely. Cystoscopy showed the bladder completely healed; this was confirmed a year later by cystoscopy. Intravenous pyelograms at this time (Fig. 4)

Fig. 3 *(left)*. Case 4. Intravenous pyelogram showing bilateral dilatation due to late irradiation changes involving intramural portions of both ureters.

Fig. 4 *(right)*. Case 4. Intravenous pyelograms one year after bilateral nephrostomy of three months' duration.

showed the pelves and ureters to be normal except for very slight dilatation of one ureter.

The disappearance of the obstruction would seem to prove that the major part of the lesion must have consisted of inflammatory reaction, since it would be unlikely that true fibrosis would have disappeared.

Case 5.—A woman of sixty-two, whose vagina was filled with epidermoid carcinoma, was given 7,800 millicurie hours irradiation by means of platinum needles. This was in April, 1936. In August, 1937, she was cystoscoped because of vesical symptoms and a few encrusted, superficial ulcers were found. Her intravenous pyelogram was normal. She was well until February, 1942, almost five years later, when an extensive encrusted cystitis was found. No shadow was seen in either kidney thirty minutes after the intravenous injection of pyelographic medium. Her non-protein nitrogen was 70 mg. per cent.

The ureteral orifices could not be identified. Nephrostomy was advised, but the patient's doctor, believing the pelvic induration to be recurrent cancer, vetoed the suggestion. The patient died of uremia. Autopsy showed bilateral hydronephrosis and hydro-ureter, but no cancer cells were found in any of the sections examined. The ureters measured 3

Fig. 5. Cross section of lower ureter, showing no appreciable change after 23,000 r. given with the 1,200 K.V. machine.

cm. in circumference; this dilatation extended down to the entrance of the ureter into the bladder. The obstruction involved the intramural portion of the ureters and was due to fibrosis which became obstructive six years after the radium treatment. It is possible that an inflammatory reaction, originating in the vesical wall and spreading laterally to involve the ureters, was a factor. Sections of this area show no cancer cells.

All of these patients were treated with radium alone; none had x-ray treatment. That x-ray treatment alone is unlikely to produce ureteral obstruction would seem to be a logical deduction from the following observation.

A man with recurring bladder cancer of a low grade of malignancy was given 23,000 r. by the 1200 K.V. machine over a period of six

and one-half months. He continued to form tumors and bled so continuously that left ureterostomy (the right kidney had been removed previously) was done. The ureter just above the bladder felt more solid than it normally should, but microscopic examination of the terminal centimeter of the upper segment showed no definite abnormality (Fig. 5).

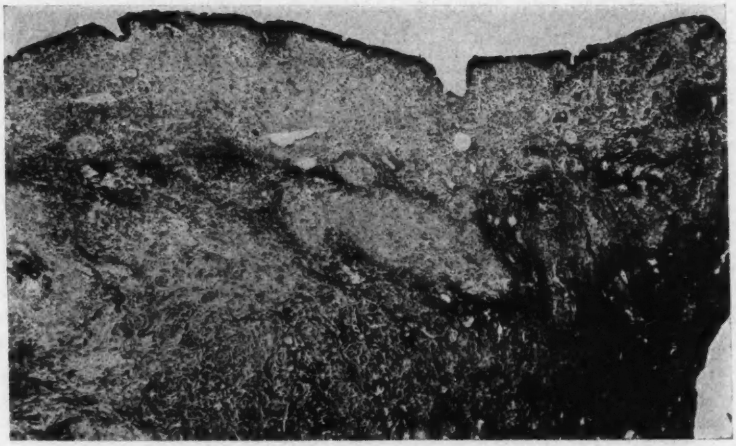

Fig. 6. Section of bladder wall from the patient whose ureter is shown in Figure 5. Note the extensive fibrosis.

The bladder was removed later, about one year after irradiation. The prostate and bladder base were firmly attached to surrounding structures, so that sharp dissection was required in order to free the lower portion of the bladder. In spite of this marked reaction to irradiation, the ureter and pelvis showed no dilatation (Fig. 6).

DISCUSSION

The frequency with which irradiation of carcinoma of the cervix or vagina is followed by ureteral obstruction is well recognized. From our observations, it would seem that irradiation by radium is the most important etiologic factor, although Daland[3] reports a case of acute ureteral obstruction on the tenth day of deep x-ray treatment for cancer of the cervix. The ureter may be invaded by cancer, but often the obstruction is caused by fibrosis of the ureter alone or by inflammatory reaction secondary to irradiation. Ever-

ett[4] reported three instances in which ureteral obstruction followed irradiation for benign lesions (the type of irradiation is not stated), and thirteen in which there was no gross evidence of cancer at the time the obstruction occurred.

If the ureter is obstructed several centimeters above the bladder, dilatation may be tried, but when the changes in the ureter are as advanced as they proved to be in the first three cases reported by us, only temporary relief may be expected. Diversion of the urinary stream, either by nephrostomy as advocated by Graves, or by ureterostomy, as we prefer, will be necessary. The three patients upon whom we did ureterostomy were unfortunate in that in two the original disease had not been controlled, but one often cannot tell whether this is the case. It is desirable to establish drainage of one kidney at least, before the renal function has been severely impaired.

When obstruction occurs at the intramural portion of the ureter and is due to inflammatory reaction originating in the irradiated portion of the bladder wall, there is good reason to hope that early nephrostomy will preserve the renal function until the inflammatory process has had time to subside. This was the situation in Case 4 and might have been duplicated in Case 5.

SUMMARY

Five cases of ureteral obstruction following radium treatment of the cervix or vagina are reported.

In two of these, microscopic examination of the ureter or of adjacent bladder wall showed no cancer cells. In one, complete restoration of the ureteral lumen following nephrostomy may be accepted as proof that the obstruction was not directly due to cancer.

From the evidence at hand, it would appear that obstruction is caused much more frequently by radium than by x-ray.

Temporary diversion of the urine by means of nephrostomy is indicated if the obstruction involves the intramural portion of the ureter and appears to be due to late radiation effect rather than to infiltration by malignant disease. If the obstruction develops at a higher point, permanent urinary diversion by nephrostomy or by ureterostomy will usually be necessary.

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HYPO-ADRENALISM (ADDISON'S DISEASE) WITH UROGENITAL TUBERCULOSIS

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The case herewith reported illustrates the advisability of the urologist, when he is treating urogenital tuberculosis, keeping in mind the symptoms of tuberculosis of the adrenals and the possibility of the co-existence of adrenal and urogenital tuberculosis.

The United States Census Bureau reports for 1939 only forty-nine deaths from tuberculosis of the adrenals and until a year or two ago I had never had a patient where a diagnosis of tuberculosis of the adrenals had been made. Partially, at least, for that reason and because of an unusually active urogenital tuberculosis, the symptoms of hypo-adrenalism were overlooked.

The patient, aged fifty-three, was sent to me July 5, 1940, with a subacute inflammation of the right epididymis and a rather marked prostatitis (Piedmont Hospital No. 58312). There was a good deal of pus in the prostatic secretion and a little pus and some gram-negative bacilli in the urine.

In 1918 he had had a tuberculous pleurisy and was sick for about six months and spent three months in New Hampshire convalescing. When he recovered he was, he said, quite well for two years. He then had a "cold abscess" in the left groin, and Dr. Michael Hoke of Atlanta found some destructive changes in the vertebræ which were evidently tuberculous. He was treated by Dr. Hoke for about a year when the abscess in the left groin recurred and again had to be drained. After that he was quite well seemingly for about eighteen or nineteen years.

The present illness began in January, 1940, with a feeling of general malaise or listlessness and a loss of appetite but almost no other symptoms.

About the only things disclosed by careful questioning were that Dr. A. N. Dykes of Columbus had found some pus in the urine at the beginning of the illness, and, a few days later, he had some cramps in his abdomen which were not severe and did not last many hours. He was told that his pulse was "fluttering," but an electrocardiogram showed no abnormality. He was in bed for a week.

He was then fairly well for about five months—until three weeks before I saw him (which was July the fifth). He was at a seaside resort and had a gastro-intestinal upset with loose stools—five in one night. Some pus was again found in the urine but the attending

physician did not explain the cause of the gastro-intestinal upset nor of the pus in the urine.

About a week later he noticed a nodule in the right side of the scrotum alongside the testicle which became tender and gradually increased in size. There were no urinary symptoms, no night sweats, and no localized pains.

When he came to me and I heard his history I was, of course suspicious of a urogenital tuberculosis. But after a careful study I concluded that he *probably* had a pyogenic infection because the condition I found was not like the usual tuberculous epididymitis. The lower (not the upper) part of the epididymis was moderately tender, firm, and enlarged to about 2x2x2.5 cm., not nodular, and the vas was not enlarged and not beaded. The prostate was symmetrical, not nodular, nor firm, and seemed almost normal except for a large amount of pus in the secretion. A careful study showed no acid-fast bacilli in either the prostatic secretion or urine.

I advised him to go back to Columbus and take some more sulfanilamide. He did this and although the sulfanilamide upset him a good deal he seemed for a while to improve, but within twenty-four days from the time I saw him he was getting worse again and Dr. Dykes sent him back to Atlanta (July 29, 1940).

On re-admission the urogenital condition was about the same—no worse, at least, and the urinary infection had cleared up. The size of the enlargement in the lower part of the right epididymis was about the same as when I saw him before.

A blood examination showed nothing abnormal except a high sedimentation rate of 102 mm. in sixty minutes. The blood pressure on admission was 110/80.

Medical and surgical consultants could find nothing to account for his complaints, but I was not satisfied that the urogenital pathologic lesion could account for his condition—for the persistent listlessness and complete lack of appetite. He would not sit up unless urged and could force himself to eat only the smallest amounts of food. He had very little fever—his temperature was less than 99 in the afternoons.

On the second of August I gave him 500 c.c. of whole blood thinking it would make him stronger and cause him to feel better. But it seemed to have made him worse for he started having fever to about 100 every afternoon, and the swelling and tenderness in the epididymis began immediately to increase.

On the ninth his blood pressure dropped to 90 and thereafter varied between 90 and 100 systolic.

After two weeks of observation and medical and surgical consultations nothing was found to explain his condition and I was urged to operate upon the epididymis since I had then for some time believed it to be tuberculous.

This I did on the thirteenth of August. In attempting to do an epi-

didymectomy I broke into a tuberculous abscess. On that account and because of the patient's age and condition, I removed the testicle as well as the epididymis. Microscopic examination confirmed the diagnosis of tuberculosis.

For a few days after the operation the patient seemed better; he was more cheerful and talked much more cheerfully, and he began eating some of his meals. But his blood pressure remained about 100 and on the third or fourth day his temperature rose to about 99.6 in the afternoons. On the fifth day he developed a pneumonia, his temperature rose much higher, and he died four days later. The autopsy showed almost no pathologic condition except the pneumonia and an almost complete destruction of both of the adrenals by tuberculosis.

Even when the patient seemed to be better for a few days after operation his blood pressure remained 100 or less, and sometimes it was below 90. He was given circulatory and cardiac stimulants, adrenal cortex, salt solution and glucose intravenously with little noticeable benefit, and also adrenalin chloride which had only a transient effect on the blood pressure.

It was not until after the operation that it was recognized that he almost certainly had tuberculosis of the adrenals, although I had suspected it, and had delayed operating upon the infected epididymis because I felt sure that something was wrong which had not been discovered. He had all the symptoms (except pigmentation of the skin) of hypo-adrenalism recorded by Osler—an insidious onset, anemia, general languor or debility, remarkable feebleness of the heart's action, and irritability of the stomach. There were also diarrhea, anorexia, and pain in the abdomen, symptoms which are frequently present, I believe, with marked hypo-adrenalism.

DISCUSSION

Dr. Frank S. Patch (Montreal, Canada): I am very grateful to Dr. Toulson for introducing a subject which for me has a great deal of fascination, even if at times the interest is largely academic. I should, however, at once disclaim the credit he was kind enough to give me, and transfer much of it to Stoerck, of Vienna, and Francois, of Paris, who have done a great deal of work on this subject as well as in the more interesting field of cystitis glandularis. This cystic condition which is to be found in the bladder and ureter and even in the pelvis of the kidney, is not a pathologic entity and should be regarded as a type of chronic infection, chronic inflammation which is usually associated with infection, and probably is derived from it.

This particular subject, ureteritis cystica, has, of course, aroused great interest since Jacoby and Joelson published the first cases diagnosed urographically. One finds, I think, a good many more cases of ureteritis cystica, even pyelitis cystica, when he is looking for them. This is particularly the case if a careful examination is made of autopsy material. Many interesting cases of the condition are brought to light when an enthusiastic pathological staff subjects the non-urological autopsy material to careful examination of the genito-urinary tract.

The etiology of these conditions has been studied by Stoerck and Francois. They are the result of chronic inflammation with metaplasia, and are not, as some say, due to embryonic inclusions. The most interesting examples are to be found in the exstrophic bladder. The infant, with such a defect, when born, shows a perfectly normal bladder mucosa, and that, I think, does away with the claim that the characteristic pictures which one sees later on such a bladder mucosa are due to embryonic inclusions. I think the first slide which Dr. Toulson showed was taken from the resected exstrophic bladder of an infant. It showed also characteristic lesions of leukoplakia and of cystitis glandularis as well as of cystitis cystica.

The treatment at times, of course, is rather difficult. Primarily, I believe one should aim at the palliation or the removal of the obstructive factor which has been responsible for the infection. That is not always possible. As far as ureteritis cystica is concerned,

dilation of the ureter at times seems to be followed by a good deal of relief. That the cysts in the ureter can obstruct the ureter, I think is fairly well proven.

I remember Dr. Wohlbach's producing a case from the autopsy material at the Peter Bent Brigham on a day when I was giving a talk on ureteritis cystica before the New England Branch of the American Urological Association, in which both ureters were almost completely obstructed by huge masses of cysts. Only in the last month, we came across some autopsy material in which some cysts in the ureter were at least a centimeter in diameter and the intramural portion of the ureter was completely blocked by masses of cysts. Dilatation in such cases would seem to have some justification and is worthy of a trial in these cases where other methods of therapy cannot be employed.

Dr. Quinby was unkind enough, in the discussion, at the meeting referred to above, to pose a question to which I was not able to give an absolutely satisfactory explanation: Why do these cases have at times such profuse hematuria? Possibly some of the gentlemen here may have the answer. I am sure Dr. Toulson and I would both be grateful to hear it.

Dr. Herman L. Kretschmer (Chicago, Ill.): I wish to discuss the paper of Dr. Toulson. Many of the older writers were of the opinion that these lesions were inflammatory and were due to infection, a fact which has not received so very much consideration among the recent writers. The frequency with which infection is demonstrated in these cases was recently reported by Dr. Warrick in *The Journal of Urology*. He showed that a large number of these cases, if studied by means of cultures, disclosed the presence of various types of bacteria.

I believe, therefore, that the hematuria and the beneficial results obtained in these cases by means of pelvic lavage with silver nitrate go hand in hand with infection.

Dr. Leon Herman (Philadelphia, Pa.): I believe this Society could make a real contribution in the matter of uterine carcinoma if we could have closer coöperation with the gynecologists in the preoperative study of these cases. At our tumor clinic at the Pennsylvania Hospital, about six months ago, one of our junior pathologists

reported a small series of autopsies, I think some twenty-five, in cervical carcinoma, with the conclusion that irradiation predisposed to fistulization of the vagina and bladder. Shortly after that, I met Dr. Charles Behney, to whose work Dr. Smith has referred, who told me that in a large series at the Philadelphia Hospital it was clearly demonstrated that those patients who had irradiation had fistulization much less frequently than those who did not have irradiation. I think that is probably now the accepted opinion.

Postoperative effects of irradiation, as Dr. Archie Dean has shown, may be delayed as long as eight years. I think the worst case of ulcer of the bladder following irradiation of the cervix that I have ever seen occurred three years after the treatment, an ulcer so serious that we had to open the bladder and could only control hemorrhage by mattress suturing. It was a very distressing, miserable thing. The patient did not have a fistula, however.

I think we do not yet know the proportion of ureteral occlusion that occurs as a result of peri-ureteral fibrosis or by actual neoplastic invasion of the muscular walls of the tube.

Also, there must be cases in which pre-operative ureteritis would be added to by x-ray or radium applied to uterine carcinoma. For this reason, I think this Society could contribute much to the progress of this phase of surgery by advocating pre-operative study of these patients. We now have a rule at the Pennsylvania Hospital that every cervical carcinoma is referred to the urological department for complete study before any treatment is advised or applied.

Each individual could adopt his own routine. We don't make urograms because they are too expensive. If there is no obvious ureteral obstruction and no retention of urine and the urine is clear and the kidney function is normal with 'phthalein, we report that the patient as yet has had no urinary injury as the result of her cervical carcinoma. Subsequently, should she develop these things, we have a standard upon which we can base an opinion with a knowledge of the condition prior to the application of the irradiation.

In so far as the relative effect of radium and x-ray is concerned, these being exactly similar agents, I think it is a matter of the means of their application, rather than the fundamentals of the physics of the agents.

DR. DAVID M. DAVIS (Philadelphia, Pa.): In connection with Dr. Boyd's failure to suspect adrenal tuberculosis, I would like to testify that that is an error which is very easy to make. The case in point was one of bone tuberculosis with enough signs of activity to justify the patient's being put on complete bed rest for a period of over a year before the fatal incident occurred. He was also exposed to sunlight in Arizona. The consequences were that the bed rest concealed any weakness which may have been present as a result of his Addison's disease, and the exposure to the sun obscured the pigmentation which was present in his case. We were just stupid about that, because it was only after he underwent a circulatory collapse that we noted there was just as much pigment in the skin under his sun-bathing trunks as there was in the exposed places.

In regard to the question of ureteral obstruction in carcinoma of the cervix, I certainly would agree with what Dr. Herman has said about the importance of the subject, but I would also suggest that it would be very wise for those who study the subject to study the older literature, thirty-five and forty years ago and longer, before irradiation treatment was used. Even at that time, Howard Kelly noted that carcinoma of the cervix and uterus was the commonest cause of hydronephrosis in women, usually bilateral. The disease itself, therefore, can cause much of this sort of change, and we must be careful not to ascribe it to irradiation without full proof that such is the case. The presence of fibrosis in the ureteral wall is not sufficient proof, since the cancer cells are often surrounded by much fibrotic reaction when no irradiation has been used.

DR. HENRY G. BUGBEE (New York, N. Y.): In 1934, I reported a number of cases of ureteral occlusion following irradiation for carcinoma of the cervix and after that we had several other cases at the Woman's Hospital in New York, where a great many cases of this type are treated. Then we began making a complete urological study of all cases before they were submitted to irradiation; also the technique of irradiation was perfected with the result that for the past five years we have not had a single case of ureteral occlusion following irradiation for carcinoma of the cervix.

DR. JOHN K. ORMOND (Detroit, Mich.): I should like to say a word about Dr. Boyd's paper. The diagnosis of Addison's disease,

when there is no pigmentation present and when the blood pressure is not unduly low, is extremely difficult. In Dr. Boyd's case the blood pressure was a little lower than average but it was not extremely low. This case is another example of the way that operation in the absence of adrenal secretion is invariably fatal.

The first successful operation in the presence of adrenal secretion was reported by Walters in 1933, and this was after adrenal extract had been made available. Since then there have been two or three other reports, and about a year ago, we had a case somewhat similar to that of Dr. Boyd's except that there was extreme pigmentation and a definite diagnosis of Addison's disease had been made. This patient came to the hospital with a draining epididymis and after treatment with desoxycorticosterone for quite a period of time, he was subjected to complete urological investigation. There was autonephrectomy on one side and a diagnosis of tuberculous epididymitis was made. Orchidectomy was done because it seemed easier than epididymectomy. He survived for a year and after death was found to have complete destruction of his adrenals and an autonephrectomy on the right side.

DR. NATHANIEL P. RATHBUN (Brooklyn, N. Y.): Discussing Dr. Smith's paper, I would like to supplement the comments made by two or three of the other speakers who suggested a careful urological survey in patients about to be irradiated. Why not add to that the periodic urological survey postirradiation? It seems to me that we might possibly postpone or even prevent some of these later complications.

DR. T. LEON HOWARD (Denver, Colo.): As far as cystitis cystica goes, ureteritis cystica, I think I have some of the earliest plates on that, away back in the 1920's. But the doctor made a remark—I thought he said they didn't occur in the pelvis of the kidney. I have one patient now whom I had excused from the Army just before I left, who has a congenital cyst of the kidneys in which cystitis cystica has practically destroyed the right kidney, involving all the calices of that kidney. Personally, I have never seen one of these patients with cystitis cystica that didn't have a colon bacilluria. This patient has bacilluria infection in his right kidney, with no infection in the left kidney. This is a young man, a physician's brother, who doubted my diagnosis of congenital cystic kidney. In most of these

cases, we have been able to clear up the bacillary infection of the colon with the sulfa preparations.

If any of you people have ever seen a radiologist destroy a ureteral caruncle with radium, you will recognize the same condition in these ureters that you get in the urethra. We have a urologist in Denver who never, apparently, destroys or removes a caruncle of the urethra except with radium, and I have inherited a great many of his cases of the damnedest strictures of the meatal mouth that I have ever known. If you put a sound in those patients the urethra will crack just like a piece of parchment.

One of the cases that Gilbert showed apparently will do the same thing with the amount of fibrosis that occurs there. They are the most painful urethral conditions that I have ever seen, and there is nothing to do for these patients that I can see, except to go carefully back and resect the urethra well up into the vagina. It makes no difference what treatment you give them, nor how often you dilate them, the urethra will crack for a few days and get relief and then will contract again and get a stricture. Why this man doesn't remove his caruncles with anything but radium has always been a mystery to me.

With regard to tuberculosis of the epididymis I have this to say. As I walked out of the National Jewish Hospital the other day, after removing a tuberculous kidney, the houseman said, "Do you know we have never had a tuberculosis of the kidney since I have been chief of the surgeons here in this National Hospital that didn't have bone lesions?"

It made me sit up and think. I have been on that service for a great many years, and as I thought back I couldn't remember a single patient in that hospital who hadn't had a bone lesion with tuberculosis while I was there. It was astounding the multiplicity of lesions that these patients have, and bone lesions were very common with renal tuberculosis.

Of course, the doctor said this patient had a source abscess. Of course, I think you never get a source abscess unless you do have a bone lesion.

Dr. W. Houston (Baltimore, Md.): I have nothing to add but I would like to refer you to Dr. Patch's article on this subject in

the *Canadian Medical Journal,* 1935. It is one of the most stimulating articles on this entire subject that can be found.

DR. GEORGE GILBERT SMITH (Brookline, Mass.): I would like to say that I agree with the discussers of our paper in every respect except with regard to one point brought out by Dr. Herman. I agree with them that pre-operative study should be done, and I agree with Dr. Rathbun that a periodic check should be done on these cases. Dr. Herman casts doubt on the difference in the effect of irradiation by radium and that by x-ray. One reason why we presented this paper was to show that apparently the radium has a much more definite effect than the x-ray, because the strength of the radium is so concentrated at the point where the ureter goes over the neck of the uterus that the effect of irradiation on the ureter at that point is intensified.

The result of the other type of irradiation, which affects the bladder wall itself, has been very well described by Dean, as we all know. I think that when a condition like that occurs in the bladder a number of years after irradiation, it is quite obvious that an inflammatory factor must be predominant. Consequently, those cases would be the ones in which one would particularly want to make an effort to save the kidney function until the inflammatory reaction had subsided.

DR. MONTAGUE L. BOYD (Atlanta, Ga.): I have nothing to add except to say that the valuable point I received from Dr. Smith's paper was the possibility of saving these patients by nephrostomy. I see a good many of these patients at the Steiner Cancer Clinic. Whether or not they are using radium less skillfully than elsewhere in the country, I do not know, but I doubt it. However, there seems to be quite a large number of ureteral obstructions in cases of carcinoma of the cervix where radium has been used, and the inclination of the men at the Clinic has been to let these people alone, let them die without doing anything for the ureteral obstruction. We would think from Dr. Smith's evidence presented here that an absorption or a freeing of this ureteral obstruction may very well occur later on, so I am going back to Atlanta and do some nephrostomies or perhaps employ some method of overcoming the effects of the ureteral obstruction.

CHEMICAL CARCINOGENESIS, DRUGS, DYES, REMEDIES AND COSMETICS

WITH PARTICULAR REFERENCE TO BLADDER TUMORS

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"This is a riddle, monstrous hard to read."

—SAMUEL JOHN STONE

It is my purpose to direct attention to the amazing number and variety of proven chemical carcinogenic agents, and to submit experimental and clinical evidence suggesting the hypothesis that the undeniable underlying cause of recurrent vesical papillomatosis may possibly be chemical in nature and extraneous in origin.

Definition.—Chemical carcinogenesis has to do with the production of malignant, transplantable, metastasizing new growths, in laboratory animals or human beings, by the action of cancer-producing chemicals introduced into the body, intentionally or inadvertently, by ingestion, inhalation, injection, or cutaneous application. Although having received but scant mention in other than special journals, the experimental achievements in this field in the past decade have been but little short of astounding. There is no more forceful method of emphasizing the recent rapid progress than by contrasting statements made by two eminent authorities, Ewing[22] and Cook,[10] in 1922 and 1938 respectively. Quoting from Ewing's second (1922) edition, *"No one has succeeded in producing cancer under conditions that are strictly experimental,"* while Cook, only sixteen years later, was fully justified in the statement, *"cancer may be produced at will in a majority of the animals treated with a variety of chemical compounds,"* mostly prepared synthetically, and of known molecular structure. It is to be noted, however, that the experimental production of tar cancer of the ears of rabbits by Japanese investigators[83] had antedated 1922 by several years, while as early as 1910 Marie[50] and co-workers had produced cancer in rats by heavy ulcerating roentgen dosage.

My own interest in chemical carcinogenesis was stimulated by a consideration of the recognized strange behavior of bladder papillomata, in that these tumors frequently are multiple and show

an amazing tendency toward re-appearance in the bladder following repeated destruction by cystoscopic fulguration at intervals through the years. The point of particular significance is that these new papillomata occur scattered here and there in various locations over the bladder mucosa, far distant from the site of the original tumor and are, therefore, to be viewed neither as recurrences nor implants, but rather as evidence of an individual inherent "papilloma-forming tendency," or of some underlying systemic cause, concerning the nature of which our knowledge is all too meager.

CARCINOGENIC AGENTS OR "INFLUENCES"

Before proceeding further, it is advisable to refer briefly to the vast literature, experimental and clinical, relating to the various "influences" having to do with the etiology of cancer. Concisely, although not entirely accurately or completely, these carcinogenic influences, or agents, may be classified as hereditary, chemical, mechanical, thermal and actinic, the latter including the carcinogenic activity ascribed to radio-active substances (Martland),[51] roentgen ray, ultra-violet light, and even sunlight (Baumann and Rusch).[4]

Our chief present interest lies in chemical carcinogenesis. Investigation in this particular field of cancer research has received tremendous stimulus during the past decade by reason of certain startling achievements in the fields of synthetic chemistry and experimental carcinogenesis, including the synthesis of a great many compounds with an amazing degree of carcinogenic potency, and the production of certain human occupational tumors in laboratory animals. Slye's[66] work, proving the inheritability either of cancer susceptibility or cancer resistance, is not necessarily incompatible with the theory of chemical carcinogenesis, in that she reconciles her conclusions with the facts related to chemical carcinogenesis by the statement that such agents as coal-tar painting, roentgen-ray burns, and other forms of "assault" may be considered to produce cancer by destroying "the cancer-resistance mechanism." Moreover, chemical carcinogenic agents and inherited susceptibility may be said to "co-operate," in that many authors have reported increased chemical carcinogenic potency, and increased cancer incidence, with susceptible strains.

ESTABLISHED FACTS

(Relating to chemical carcinogenesis, and verified by incontrovertible clinical and experimental evidence, as related below)

1. There are many industries with proven occupational cancer hazards, due to prolonged contact of the workers with various chemicals, known and unknown. In such industries, experiments in carcinogenesis with human subjects have been inadvertently carried out.

2. Recognized cancer-producing chemicals, the potency of which has been unquestionably established by animal experimentation, are numerous and varied as to chemical composition.

3. The chemical etiology of bladder tumors of anilin dye factory workers is established beyond question. Infinitesimal daily dosage is adequate.

4. By the administration of an anilin dye "intermediate" (commercial beta-naphthylamine), the experimental production of bladder tumors in dogs has been achieved.

5. Spontaneously-occurring bladder papillomata, clinically observed, show certain surprising characteristics, such as multiplicity, and a well-defined tendency toward repeated reappearance (elsewhere in the bladder) after destruction by cystoscopic fulguration, and not infrequently undergo malignant degeneration. In these respects, as well as histologically, spontaneously occurring bladder papillomata bear a close resemblance to those produced experimentally and by occupational contact.

6. There are numberless individuals who are habitual, through-the-years users of a great variety of proprietary "remedies" and cosmetic concoctions, ingredients unknown.

EVIDENCE CONFIRMING FACTS

Occupational Cancer

Occupational cancer among workers in certain industries, recognized as occurring with such frequency and regularity as to exclude mere coincidence, served first to direct attention to the existence of chemical carcinogenic agents. The classical example of these so-called occupational tumors, first to be recognized as such, was the scrotal cancer of chimney sweeps, due to chronic contact with soot, and described by Pott[55] as early as 1775. There is a voluminous literature relating to occupational cancer occurring among

workers in many and varied industries contacting coal-tar[32] and tar-distillation products (pitch, creosote, anthracene), shale oil,[64] various crude mineral oils,[35] paraffin,[47] chromium,[1] radio-active substances,[51] beta-naphthylamine[38] and other miscellaneous substances, proven or suspected, including nickel,[38] zinc chloride,[23] asbestos,[37] potassium nitrate[56] and silica, iron and copper dust.[74] The fate of the pioneer roentgenologists is familiar to all. Other conspicuous specific examples, proven beyond doubt, include the bladder tumor of anilin dye workers,[25, 58] scrotal cancer of cotton mule spinners,[68] resulting from saturation of the clothing with lubricating oil, esteogenic sarcoma of luminous watch dial painters,[51] lung cancer of Schneeberg and Jachimstal miners,[71] and lip cancer of fishermen,[5] due to holding between the lips the wooden needle threaded with twine treated with a tar-creosote mixture. This incomplete listing serves the purpose of showing that the occupational tumor hazard is anything but mythical.

Miscellaneous Chemical Carcinogenic Agents (Experimental)

Observations relative to the carcinogenic potency of *coal tar* (as demonstrated by chronic occupational contact) have led to a tremendous amount of experimental work and a voluminous literature upon this subject alone. Skin cancer of the ears of rabbits, following prolonged coal-tar painting, was first reported by Yamagiva and Itchikawa[83] in 1915, and by Tsutsiu,[73] with mice, in 1918. Numerous investigators, by prolonged and repeated application of coal tar upon the skin of laboratory animals and also by injection methods, have succeeded in producing not only skin cancer, but also malignant metastasizing transplantable new growths, involving various remote internal organs. Rabbits and mice have been found to be peculiarly susceptible to experimental coal-tar cancer, while rats, fowls, and dogs are almost completely resistant. Two most comprehensive surveys of this subject, covering the literature up to 1926 and 1932 respectively, are those of Woglum[79] and Eggers.[20] Marked variations in carcinogenic potency have been recognized in tars from different sources, or prepared from the same coal by different methods or at different temperatures. Through a period of years, vast effort has been expended in attempts to determine the exact constituent or constituents of the amazingly complex mixture of hydrocarbons known as coal tar responsible for carcinogenic properties, and resulting finally in the isolation and also the synthe-

sis, of 1:2 benzpyrene (an exceedingly potent carcinogen of the hydrocarbon group to be referred to later) achieved by Cook, Hewett and Hieger[12] in 1933.

Roffo[61] has recently reported obtaining by distillation of tobacco tar, a highly carcinogenic substance having the spectographic characteristics and the flourescence of 1:2 benzpyrene, although these experiments were not confirmed by Suguira.[69] As long ago as 1925, Kennaway[41, 42] described carcinogenic tar-like products resulting from the distillation of the various organic substances including acetylene, isopyrene, yeast, cholesterol and even human muscle and human skin. His method consisted of passing the volatile products resulting from slow heating of these substances through a hydrogen-containing tube heated to 780°-920°, and collecting the "black, oily residue" in cooled receivers. As pointed out by Twombly,[75] the transformation by Kennaway of the hydrocarbon acetylene into a carcinogenic substance constituted an important step, in that is was thus possible to classify the latter as a pure hydrocarbon.

Marked carcinogenic potency is also possessed by *various crude mineral oils* as originally demonstrated in lesions developed by workmen exposed to the crude products obtained by the distillation of oil-bearing shales of Scotland (Leitch).[46] Twort and Lyth[76] have described the concentration of carcinogenic materials in mineral oils by distillation processes. The obvious hypothesis that there may be danger of carcinogenesis resulting from the extensive therapeutic use of mineral oils is refuted by no less an authority than Francis Carter Wood,[80] who bases his opinion upon the statistical evidence afforded by the "thousands of tons" annually consumed clinically, internally and as ointment, without increase in cancer incidence; also upon extensive and convincing mice-painting experiments carried on with standard mineral oil products. The apparent discrepancy between this report and the abundant conclusive evidence of the carcinogenic potency of various crude oils has been explained[35, 64] by the action of acid employed in the bleaching and purification processes in destroying the carcinogenic constituent. Experimental confirmation of this has been proved by Twort and Fulton,[77] who rendered carcinogenic oils impotent by extraction with sulphuric acid. That the Report of the Manchester Committee on Cancer (1929),[49] concerning carcinogenic substances in oils

and tar, should refer to an attempt to discover a "safe lubricating oil" is ample evidence of the incidence of crude oil cancer in England.

Certain *azo dyes* are of a great deal of interest. As long ago as 1906, Fisher[28] made the sensational announcement that he had produced a typical epithelial proliferation by the injection of scarlet red into the ears of rabbits. Although these cellular proliferations tended to recede and proved to be non-malignant, this work led to the clinical use of scarlet red as an epithelium stimulant, as advocated by J. Staige Davis,[17] and later to the recognition (by Hayward)[34] of amino-azotoluene as the active portion of the scarlet red molecule. This subject has been reviewed in a very interesting manner by Shear.[65] Using amino-azotoluene in a series of mice injection experiments, this author was able to produce primary liver cell carcinoma in all mice surviving for one year, and succeeded in transplanting these tumors through several generations. This followed the work of Yoshida,[84] who produced liver cancer in rats by feeding experiments with the same dye. With azotoluene, however, Otsuka and Nagao[53] produced papilloma and carcinoma of the urinary bladder, also in rats, thus demonstrating tissue specificity, dependent upon a relatively minor change in the molecule. Among a large number of related azo dyes tested, Kinosita (quoted by Cook and Kennaway)[15] succeeded in producing liver cell cancer, also with the mono-acetyl and diacetyl derivatives of amino-azotoluene, and with p-dimethylaminoazobenzene, the dye known as "butter yellow," formerly extensively employed in the coloring of foodstuffs. Otsuka (quoted by Shear)[65] produced papillomatous growths of the stomach in mice fed diazoaminobenzol.

Carcinogenic properties have been ascribed to certain *physiologic chemicals* produced within the body, among these acetylcholin, vitamins, and estrus-producing substances. For instance, Hall and Frank[33] reported "an inordinate number of tumors which developed in various animals" during prolonged acetylcholin administration. Eller and Wolff[21] reviewing the literature, concluded that "the evidence that experimental tumors can be produced by a diet rich in vitamins is inconclusive," although stating that the majority of authors consider vitamin excess to be a factor in tumor initiation and tumor growth. Cramer[14] considers the carcinogenic potency of estrogenic substances, in producing mammary cancer in mice,

discovered by Lacassagne[43] to be "based upon evidence which is incontrovertible." Eller and Wolff, reporting a certain commercial estradiol-containing face cream which "produced cancer in animals, as well as other profound systemic changes, when applied on the skin in one-fifth the amount recommended for daily use by women," have quoted numerous warnings from authoritative sources against indiscriminate, prolonged use of estrogen-containing ointments. The chemical grouping known as the phenanthrene nucleus, possessed in common by the most potent of the carcinogenic hydrogens to be referred to later, is "widely distributed in nature in a variety of physiologically important compounds, including cholesterol, vitamin D, the bile acids and the sex hormones." (White).[81] Very recently, Auchincloss and Haagensen[2] have commented upon the unrestricted and promiscuous use of estrogenic substances in cosmetics and in the treatment of a wide variety of clinical disorders, and have pronounced this subject "a matter for serious consideration." Relating a detailed case history of carcinoma of the breast, these authors presented plausible reasons for considering it "entirely possible, indeed even probable" that estradiol benzoate, in large dosage, was a contributing cause, and advised caution in dosage, especially in case of familial predisposition. Moreover, this topic has been considered of sufficient importance to have appeared in the editorial columns of the *Journal of the American Medical Association*,[19] where a distinct note of warning has been sounded.

There are recognized and suspected inorganic carcinogenic agents. As long ago as 1888 Hutchins[40] called attention to multiple primary skin cancer, often located upon the hands and feet, resulting from long-continued oral administration of potassium arsenite, in the treatment of psoriasis. This clinical observation was confirmed experimentally by Leitch and Kennaway,[48] who reported a metastasizing carcinoma in a mouse, appearing locally following prolonged skin painting with Fowler's solution. The original work of Michalowsky in producing teratoma of the testis of the fowl by injections of zinc chloride has been confirmed by Bagg[3] and by Falin,[23] the latter obtaining the same results with zinc sulphate. Prunes[56] has recently reported cancer from potassium nitrate, referred to as salt-petre disease, occuring in this industry in Chile. Turner and Grace,[74] in a well-written and convincing analysis of

the cancer statistics, over a ten-year period, of the city of Sheffield ("the home of the metal grinding industry"), demonstrated a greatly increased respiratory tract and alimentary tract cancer incidence among machinists, foundry workers, grinders and sandblasters, as compared with white collar workers, which they ascribe to the inhalation or ingestion of silica, copper or iron dust. Suntzeff et al.[70] produced sarcoma in mice by the injection of a buffered solution of hydrochloric acid.

Carcinogenic agents of *vegetable origin* have likewise been the subject of investigation. The high incidence of abdominal cavity sarcoma reported by Rowntree and associates,[62] in rats fed crude wheat germ oil, has not been confirmed by Rider,[60] or by Ginzton and Connor.[30] Carcinogenic properties ascribed to sesame oil have been referred to by Schiller.[63]

Other miscellaneous compounds, chemically unrelated, which have been shown to possess carcinogenic properties include triphenylbenzene, tetraphenylmethane (Morton et al.[52]) and beta-naphthylamine, the latter being of particular interest from both clinical and experimental viewpoints, in having been shown to be the agent responsible for the bladder tumor of anilin dye workers. Schiller[63] has reported the production of rat sarcoma by the subcutaneous injection of the dye light green F. S. New growths have also been reported following glucose injections.

Diet as an influence in carcinogenesis has been a subject of theory and controversy since the time of Galen. Deficiency, or excess intake, of many of the more common articles of diet, including even such items as salt and water, has been blamed and exonerated from time to time. Reimann[59] is inclined to dismiss the subject with the theory that all living things (plant and animal) have cancer, but no article of diet in common. A recent unconfirmed report[52] has appeared of carcinogenic substances (as determined by mice painting experiments), obtained from roasted food—particularly roasted meat and browned butter. The carcinogenic potency of any given staple article of diet awaits demonstration.

Carcinogenic Hydrocarbons

The most extraordinary and the most potent carcinogenic agents known are members of a group of complex hydrocarbons, synthesized, described and tested, during the past decade, by Cook, Ken-

naway and associates[15] in the Royal Cancer Hospital, London, and by Fieser and associates[26] at Harvard, and subsequently investigated in great detail as to carcinogenic properties by many workers, including Haslewood, Hewett, Hieger, Mayneord, Bachmann, Bonser, in England, and in America, M. Fieser, Shear, Newman, Seligman, Hershberg, and many others. Resulting from these investigations, a voluminous literature has appeared dealing both with chemical and biologic phases of this subject.

This group of hydrocarbons includes particularly cholanthrene, methylcholanthrene, benzpyrene, benzanthracene, and a great number of related synthetic compounds showing marked variations in carcinogenic potency based upon seemingly minor substitutions in the molecule. In this experimental work, in general, the evaluation of the carcinogenic potency of a given compound has been based upon cancer incidence and rapidity of cancer development in mice-painting experiments. Methods of standardization of carcinogenic activity have been described in great detail by Twort and Twort.[78] Cook and co-workers[13] were "led to the discovery of the carcinogenic properties of benzanthracene by the resemblance of the fluorescence spectrum of this substance to that of certain carcinogenic mixtures" such as tar and shale oil, as described by Hieger[36] in 1930. The potency of benzanthracene in stimulating cell proliferation in tumor tissue culture has been demonstrated by Creech.[16] Methylcholanthrene, one of the most potent of these compounds, is chemically related to, and has been derived from, human bile acids, by Fieser and Newman,[27] and also by Cook and Haslewood,[11] thus suggesting the hypothesis that cancer-producing hydrocarbons may possibly be formed in the human body as the result of abnormal metabolism of physiologic chemicals normally present. Cholanthrene and methylcholanthrene, painted on the skin of mice in 0.3 per cent benzene solution have been reported to produce epitheliomata in as short a time as seventy or eighty days. Following subcutaneous injections of methylcholanthrene in mice, Bonser and Orr[6] have reported a high incidence of malignant tumors including both carcinoma and sarcoma involving various internal organs. Such experiments have been duplicated by many workers. As reported by Dobrovolskaia-Zavadskaia,[18] the infinitesimal unit dose of benzanthracene of two and one-half millionths of a gram is capable of

producing sarcoma in a mouse. The synthesis and the investigation of the carcinogenic hydrocarbons, resulting from years of tireless cooperative effort by the London and Harvard groups, may be said to constitute the most brilliant chapter in the history of cancer research.

An excellent general summary of this subject was presented in the 1939 Guiteras Lecture by Caldwell.[8] For a highly technical discussion, dealing with molecular structure in its relationship to carcinogenesis, the reader is referred to the review by Cook and Kennaway[15] and for a most entertaining and instructive historical survey, from the lay viewpoint, to the recent article in *Scientific Monthly* by Twombly.[75]

Anilin Bladder Tumor

The so-called anilin bladder tumor of dye factory workers is by far the most interesting known occupational tumor, because so frequently observed and because occurring in an internal organ remote from any possibility of direct contact, thus suggesting tissue specificity. This occupational tumor has been known and recognized since its description by Rehn[58] in 1895, although not appearing in America until after a latent period of ten to fifteen years following the migration of the dye industry to America, as a result of changing conditions in the chemical industry due to the first World War. As reported in 1938, more than eighty cases had appeared in one American plant alone, while the total number of reported cases here and abroad (more than five hundred) is obviously greatly exceeded by the total incidence. Observation has shown that the victims are not those handling the finished product, but those who, for a long period of years, have been exposed to, or come in contact with, certain "intermediate" chemicals, particularly beta-naphthylamine; also possibly anilin and benzidine. Obviously, the daily dosage of this carcinogenic agent, unintentionally and unknowingly ingested, inhaled, or absorbed, is exceedingly minute. These chemically produced bladder tumors are grossly and microscopically identical with spontaneous bladder tumors, and have similar clinical behavior. They may be single or multiple. Histologically, all graduations from simple benign papillomata to highly malignant infiltrating carcinomata have been described in detail by Gay[29] who considers that "anilin tumors are anatomically

identical with those of unknown origin." The majority of these tumors develop between the tenth to the twentieth years of exposure, although some authors consider one to two years adequate, in that tumors may appear years after cessation of exposure.

Following the lead suggested by dye plant statistics, indicating chronic exposure of a large percentage of workmen to beta-naphthylamine, Hueper and co-workers[39] have succeeded in the experimental production of bladder tumors in dogs by the oral administration of this intermediate, thus affording incontrovertible experimental proof, substantiating the statistical clinical evidence, that anilin bladder tumor is an occupational lesion resulting from chronic contact with a chemical carcinogenic agent. These dog bladder tumors likewise may be single or multiple, and include benign papillomata and infiltrating metastasizing carcinoma. The authenticity of this amazing experimental achievement is not open to question. According to Hueper, beta-naphthylamine is not excreted in the urine as such, and precise information as to the "exact nature of the carcinogenic agent or as to the mechanism of its action on the cells of bladder mucosa" is lacking. Cook and associates have suggested the conversion in the body of beta-naphthylamine into 3:4:5:6 dibenzcarbazole, of known carcinogenic potency, although this substance has not been demonstrated in the body after exposure to beta-naphthylamine. Whatever the carcinogen may be, there is a difference of opinion as to whether action takes place through urinary contact (Hueper[38]) or via the blood stream (Ferguson[24]).

POSSIBLE UNRECOGNIZED CARCINOGENS

The preceding extensive, but by no means complete, enumeration of achievements in chemical carcinogenesis is submitted by way of directing attention to the multiplicity and the variety (with respect to molecular structure) of proven chemical carcinogenic agents. This evidence suggests the possibility that the genesis of "spontaneous" bladder tumors may bear a relationship to chronic contact with unrecognized chemical carcinogenic agents which we unknowingly encounter in the routine of our daily lives. The variety of ways in which such chemicals and drugs may be contacted, resulting in the ingestion, inhalation, or absorption of daily minute dosage, either intentionally or inadvertently, is as infinite as is the number of chemicals and drugs available. In addition

to accidental contacts and occupational contacts, there is the enormous list of drugs included in the pharmacopœia, dispensed by physicians through legitimate prescription channels. Although ingredients of prescriptions be known, and although *Pharmacology* fully described the action of unit dosage of various drugs, we have no precise knowledge as to the possible remote biologic consequences of cumulative dosage, assimilated frequently and regularly through the years.

"Concoctions"

If the above is true, it is then pertinent to inquire what is known about the remote cumulative effects of the appalling number of patent medicines, "remedies," and cosmetics, dosage and ingredients *un*known, and distribution uncontrolled? What about the myriads of concoctions of mystic formulæ, glorified by ornate wrappings and containers, gaudily proclaimed through the mails, and in otherwise respectable publications, and made available at fancy prices to the uninformed, helpless and trusting (although indifferent) consumer, by blatant quacks and racketeers—and others. How about the endless list, including proprietary cathartics, sedatives, nervines, digestants, tonics, anodynes, stimulants, elixirs, emulsions, lotions, powders, creams, ointments, gargles, sprays, astringents, pastes, paints, depilatories, hair tonics, hair dyes, dandruff cures, obesity cures, bust developers, bath salts, perfumes, et cetera, ad infinitum? This incomplete list includes only the general groups; not the trade names, the number of which is legion. Incidentally, less than an average ten cents of the cosmetic consumer's dollar goes for ingredients and containers,[45] the balance for glamour. Those further interested in the cosmetic racket are referred to the aptly entitled chapter on cosmetics, "Your face is my fortune," also referred to as "The Skin Game," in Solomon's[67] "The Traffic in Health," also to "Nostrums and Quackery and Pseudo-Medicine," by Camp.[9] Of the proprietary and trade-name remedies, many have been proved to be definitely injurious, while many others have known toxic ingredients. To give one example only, phenolphthalein, a coal tar derivative of proven toxicity (Solomon[67]) is an ingredient of more than 125 proprietary laxative preparations, in most instances disguised in some sort of confection and advertised by each pharmaceutical house under its own trade name, many of which are familiar household words. The truth is that the

remedy racket is aided and abetted by the physician for the simple reason that less mental effort is required to write trade names than prescriptions. In this connection, the great service rendered an indifferent public by the Bureau of Investigation of the American Medical Association in combating the nostrum evil, and in uncovering fraudulent advertisers, deserves far more commendation than has been received.

But the whole story has not been told. There remain the bewildering alphabet of vitamins, the sex hormones (with nomenclature hopelessly confused by trade names) and the tremendous list of anilin dyes used in the coloring of foodstuffs and fabrics.

HYPOTHESIS

The recognized tendency of bladder papillomata toward multiplicity and re-appearance indicates an inherent "tumor-forming tendency," or an underlying systemic cause, an explanation of which upon an extraneous chemical basis would not be wholly without experimental and clinical precedent. Since there are a great many chemical carcinogens of recognized and known potency, it is entirely reasonable to consider that there are many others as yet unrecognized as such and perhaps included among the various chemicals with which we come in daily contact. In this connection may be mentioned the work of Suntzeff, Babcock and Loeb,[70] who produced sarcoma in mice by the injection of a buffered solution of hydrochloric acid, and who concluded there is "little doubt that chemically relatively simple substances, other than the well-known carcinogenic compounds, are able to produce sarcoma after long-continued injection." According to these authors, Nonaka produced sarcoma in rats and mice by glucose injections.

Since the number of chemical ingredients employed in prescriptions, proprietary remedies and cosmetics surpasses enumeration, it is easily conceivable that this list may include carcinogenic agents as yet unrecognized as such. And since the extent of the "remedy" and cosmetic traffic, as well as the number of addicts, surpasses comprehension, it is not inconceivable that the occasional, chronic, through-the-years user of these various mystic concoctions may become the victim of chronic chemical poisoning by carcinogenic agents. In this connection, it is not illogical to assume that the genetic factor plays a major role, as is the case with laboratory

animals. I repeat that infinitesimal daily dosage, long continued, has been proved adequate in many industries. Moreover, chronic poisoning from cosmetics,[44] apparel dyes and hair dyes,[54] producing both dermatologic and systemic symptoms, is too well recognized to require proof.

Of major importance in this connection is the amazing array of tabulated experimental evidence recently submitted by Reding[57] concerning unsuspected carcinogens included among the many anilin dyes commonly employed in the coloring of foodstuffs and as therapeutic agents. Although only relatively few of the very large number of anilin products thus used have been investigated, no less than about thirty ("une trentaine") of these have been shown to possess definite carcinogenic properties, as determined by direct experimental evidence, quoted by Reding. Chief among these are certain naphthylamines, carbazoles and chrysenes, certain acridine compounds, and a large number of azo dyes, including p-dimethylaminoazobenzene (butter yellow), o-aminoazotoluene (anilin yellow) and its diacetyl derivative. The last named of these, diacetylaminoazotoluene (Dimazon), is Council-accepted. Browning, Gulbransen and Niven,[7] using the benzoyl-amino styryl compound known as "styryl 430" in the experimental treatment of trypanosome infection, produced sarcoma in mice by a single subcutaneous injection. Reding's tabulation proves nothing whatever, but indicates the possibilities, even though permitting the cynical observation, made without consideration of the multiplicity of causes of cancer, that cancer records antedate synthetic chemistry by untold numbers of centuries.

CLINICAL OBSERVATIONS

With these thoughts in mind, I have taken occasion to interview a number of bladder tumor patients with respect to drug and cosmetic habits. For no logical reason other than the behavior of papillomata (suggesting chronic systemic poisoning as outlined above), and perhaps quite improperly, I have excluded frank carcinoma and limited this inquiry to the last few bladder papilloma patients recently observed.

Of seventeen such patients interviewed, there were seven giving a history of through-the-years drug or cosmetic habits, in addition to three others relating chronic occupational chemical contacts.

For periods of time ranging from "several" up to twenty and even twenty-five years, these ten patients, among them, had been chronic, regular consumers of drugs or mixtures marked as "Glycothymolin," "Amolin," "Veracolate," "Nonspi," "S.T.-37," as well as an unidentified hair "creme," mineral oil shampoo and special hair tonic. An incomplete enumeration of the ingredients of these various "remedies" and cosmetics includes, phenolphthalein, hexylresorcinol, tincture benzoin, benzyl benzoate, sodium benzoate, thymol, menthol, glycerine, aluminum chloride and iron chloride, to say nothing of the occupational chemical contacts, including potassium cyanide, turpentine, amyl acetate, lubricating oil and castor oil! I hasten to concede that it is most unlikely that these ten patients represent a true cross section, and to point out the obvious absurdity of attempting to draw conclusions from these meager observations. It is possible, however, that *an analysis of the results of a very large number of such interviews might direct suspicion against certain chemicals recurring in various concoctions with conspicuous frequency;* possibly sufficient suspicion to justify animal experimentation with the chemicals indicated.

Likewise merely suggestive is the case report by Goeckerman and Wilhelm[31] recording the demonstration of arsenic crystals by microchemical studies (by Osborne's method) in sections from a ureteral papilloma and a vesical carcinoma, removed from a patient with a history of arsenic ingestion in the form of Fowler's solution over a several-year period. This patient also showed typical arsenical keratosis of the palms and soles.

COMMENT

The question naturally arises as to what there is to be done about the cosmetic racket, the answer being little or nothing, because the chief and insurmountable obstacle lies in the gullibility of the consumer. I refer to my wife and yours; and suggest that each of those unconvinced invoice the contents of the medicine cabinet of his own residence. From this approach, the situation would seem to be hopeless, although the Federal Food, Drug and Cosmetic Act, enacted by the 75th Congress, containing strict regulations with respect to misbranding or labeling which is "false or misleading in any particular," is a step in the right direction.

If I have succeeded in creating the impression that it is my con-

sidered opinion that cosmetics cause cancer, then I have failed utterly. It has been my purpose to direct attention to the multiplicity and the wide variety of chemical carcinogenic agents, proven and suspected, and to suggest the possibility that dangerous chemicals of this class, unknown and unsuspected, may be masquerading as innocent ingredients of prescriptions, and "concoctions." This presentation is intended merely to be thought-provoking.

Anticipating criticism, if not ridicule, I concede: That the skeptic is doubtless right; that it is exceedingly unlikely that there are carcinogens masquerading as innocent ingredients; that there are countless "remedy" addicts without symptoms of cancer; that there are countless cancer victims without drug or cosmetic habits; and that cancer records antedate synthetic chemistry, and cosmetic racketeers, by untold centuries.

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PRESACRAL SYMPATHICOBLASTOMA IN AN INFANT CAUSING URINARY OBSTRUCTION

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The presentation of a single case simply because the condition is rare is seldom justified. However, in this instance the unusual location of a tumor of this type and its successful removal may warrant its being recorded. Neuroblastomata sympathicum or sympathicoblastomata are usually primary in the adrenal medulla but they do occur in other areas, and in practically all of the reported cases the outcome has been fatal. However, Farber's[7] recent survey at the Children's Hospital in Boston has forced us to modify the almost hopeless prognosis and this case calls your attention to the possibilities of treatment when a tumor of this type is discovered.

The presacral origin of the tumor is of interest. The terms presacral or sacrococcygeal tumors, or tumors ventral to the sacrum, have a certain connotation. They immediately bring to mind that this area is sort of a burying ground or repository for remnants cast off in the complex embryonic development of the terminations of the intestinal tract and central nervous system. These remnants may later be a source of complex tumors such as those which combine nerve and intestinal elements and are supposed to arise from the neurenteric canal which in the very early embryo connects the neural tube with the hind gut.

Then there are the Middledorf tumors arising from the remnants of the postanal gut, the terminal portion of the hind gut which is pinched off in the formation of the rectum.

Sacral teratomata are not uncommon and they have a tendency to produce a great variety of rudimentary organs; in fact, they are the most prolific of any in the production of rudimentary organs. Secondary changes in these tumors give rise to sarcomata of various types.

Although some of these complex growths may have nerve elements in them there is another group of strictly neurogenic tumors about the sacrum, outside of the cerebrospinal axis and peripheral nervous system that originate in remnants from the development of

the vertebral column, the spinal cord and the sympathetic nervous system. The commonest of these are the chordomas which arise from remnants of the notochord, the anlage of the vertebral column. Ependymal cells which in early embryo form a large part of the neural tube but which remain only as the ciliated columnar cells lining the central canal of the cord and the ventricles, may give

Fig. 1. Cystogram showing bladder displacement.

rise to presacral ependymomata which adds to the perplexing problem of the classification of the bizarre growths in this region.

Tumors arising from the formative cells of the sympathetic nervous system are usually primary in the adrenal medulla but they do arise in other areas, cervical, retropleural, retroperitoneal and rarely sacral, as in this case. The histogenesis and prognosis are the same in the extra-adrenal as in the adrenal growths.

The urologist's interest in these presacral tumors lies in the fact

that he may be the first to see these patients because of dysuria, a not uncommon early symptom from either direct impingement of the tumor on the lower urinary tract, or involvement of the sacral and pelvic nerves.

CASE REPORT

The patient, a male infant three weeks old, was admitted to the Children's Orthopedic Hospital because he had been unable to urinate since birth. There was a catheter fixed in the urethra and the attending physician, not unreasonably, had made a diagnosis of congenital valves of the posterior urethra. However, there was a tumor in the lower abdomen extending out of the pelvis which was obviously not a distended bladder because the indwelling catheter was draining. On rectal examination a mass could be felt which filled the hollow of the sacrum and extended forward to the symphysis.

Although a Coude catheter could be passed with some difficulty, attempts at cystoscopy were discontinued because of marked obstruction and angulation in the posterior urethra. A cystogram showed the bladder to be displaced upward and to the left (Fig. 1). A tentative diagnosis was made of sacrococcygeal teratoma.

At operation the tumor, which was exposed through a midline suprapubic incision, was found to be a vascular, partially necrotic, retroperitoneal mass arising from the hollow of the sacrum and completely filling the pelvis (Fig. 2). The posterior peritoneum was opened and the tumor freed as far as possible, but it was difficult to get at its base so it was resected and a portion left attached to the anterior surface of the sacrum. The posterior peritoneum and abdomen were closed rapidly because the child's condition was poor. However, the patient recovered and two weeks later a rectal examination showed that there was still a portion of tumor about 5 cm. in diameter attached to the sacrum.

A diagnosis of neuroblastoma was made by Dr. Mosiman, pathologist at the Children's Orthopedic Hospital and confirmed by Dr. C. L. Connor, professor of pathology at the University of California Medical School, whose report was as follows.

Microscopic Description: The section stained with hematoxylin and eosin shows a very cellular tumor with a stroma of connective tissue and blood vessels. The tumor cells lying in irregular lobules formed the interstitial tissue. The cells were quite small and round and had rounded, quite uniformly sized nuclei which were hyperchromatic. In the nuclei the chromatine material, while dense, forms no particular pattern and the nucleoli can generally be distinguished. The cytoplasm is scant or non-staining. In places the cells are grouped in a circular manner, one or two layers surrounding a space filled with very faintly staining fibrillæ, running from cell to cell across the center. These are

true rosettes with the fibrillary material forming characteristic structures in neuroblastomas. Numerous mitotic figures are seen and the tumor is obviously malignant. From the histology this tumor should have arisen in the anlage of the adrenal medulla and from its position one suspects that it grew into the sacrum by extension from pelvic lymph nodes rather than that it had arisen from the sacrum. However, such tumors may arise from other sympathetic analgens or from

Fig. 2. Large vascular retroperitoneal tumor arising in the pelvis.

misplaced accessory adrenal medullary tissue. *Diagnosis:* Neuroblastoma (Fig. 5).

This diagnosis made the outlook almost hopeless because up to that time there had apparently been only one surgical cure (Lehman, 1917)[8] and according to the reported cases, irradiation was of little value. However, it was felt that x-ray therapy would do no harm and 1260 r were given in twelve treatments over a period of two months. At the end of the time, greatly to our surprise, the remainder of the tumor had completely disappeared as far as could be determined by rectal palpation and there have been no demonstrable recurrences since. The child is well four years after operation (Fig. 3).

DISCUSSION

A sympathicoblastoma or neuroblastoma sympathicum is a highly malignant tumor arising from the undifferentiated formative cells

of the autonomic and chromaffin systems. They are tumors of infancy or early childhood and are not uncommon. At the Children's Hospital in Boston in each of the last ten years there have been four cases of sympathicoblastoma with growths in all locations of the body to three cases of embryoma of the kidney or Wilm's tumor.[7]

Fig. 3. Cystogram four years after operation.

Tumors of the sympathetic nervous system are characterized by a definite relationship between the age of the patient, the cellular differentiation of the tumor and the degree of malignancy. The older the patient, the higher up the developmental scale and the more benign the tumor. They may be composed of any of the types of cells which take part in the formation of the sympathetic nervous system, either alone or in combinations. However, the dominant cell determines the classification and indicates the degree of malignancy.

To understand the malignant member of this group, the sympathicoblastoma, a brief review of the histogenesis of the autonomic system is necessary (Fig. 4).

The sympathogonia is the parent cell of the sympathetic primordia. It is small with little cytoplasm and a deeply staining nucleus, and its resemblance to a lymphocyte has led to the errone-

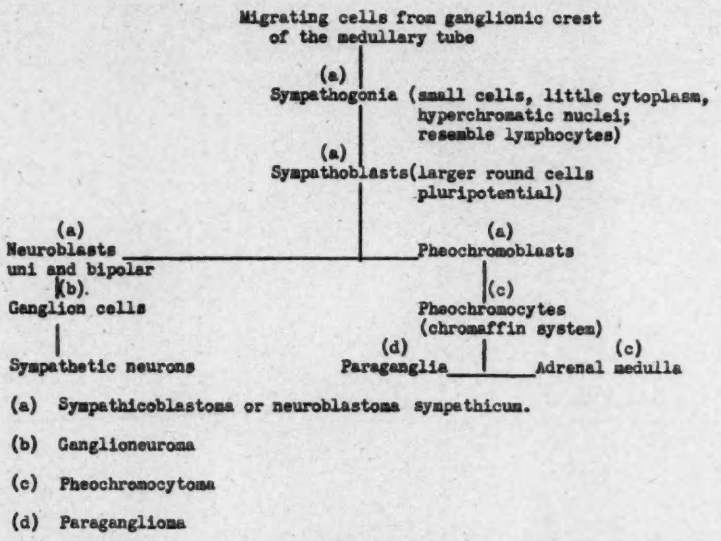

Fig. 4. Primordia of the sympathetic nervous and chromaffin systems.

ous diagnosis of lymphosarcoma in many of the undifferentiated tumors composed largely of sympathogonia. In fact, most of these tumors were called lymphosarcomata until Wright,[11] in 1910, conclusively demonstrated that they were neurogenic and gave them the term neuroblastoma or sympathicoblastoma. Later the sympathoblasts become polygonal, develop fibrils and form ganglion cells from which the sympathetic neurons are derived.

The sympathoblasts, however, are pluripotential. Some of them do not develop into ganglion cells but show an affinity for chromates and later give rise to the pheochromocytes, the formative cells of the chromaffin system consisting of the adrenal medulla and the

paraganglia. The latter form the carotid body, the coccygeal gland and are found in the submucosa of the appendix and the small intestine where they may give rise to the carcinoid tumors or paraganglioma of these structures.

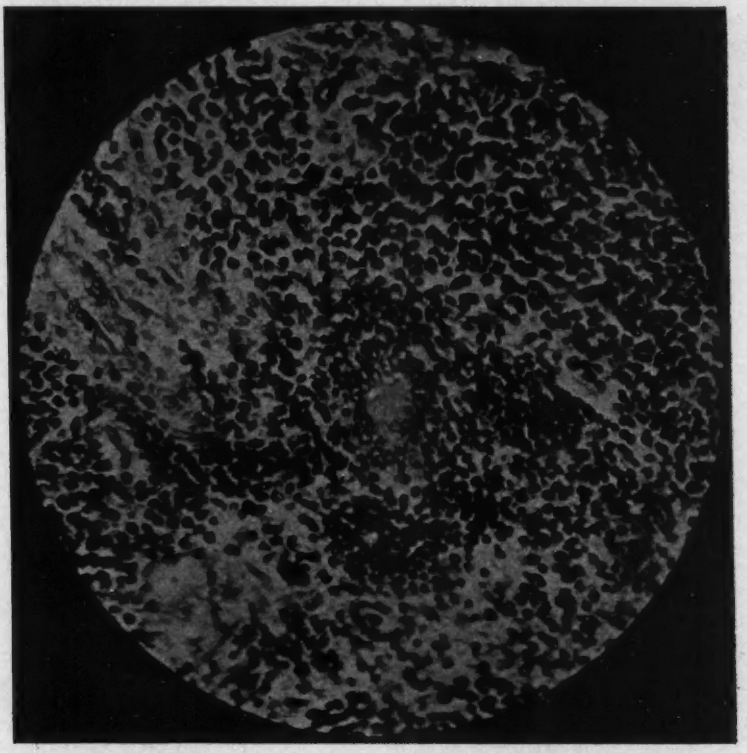

Fig. 5. Histologic preparation made from tumor removed at operation showing the smaller sympathogonia and the larger sympathoblasts. There are several rosettes and a few fibrils. The tubular arrangement in the center of the section is a pseudorosette.

Tumors arising in this system may range from the completely undifferentiated growths made up of sympathogonia only (rare), through an intermediate group containing sympathogonia and the larger sympathoblasts in various proportions (the commonest type),

to the simple and generally benign growths composed only of ganglion cells, the ganglioneuroma.

The characteristic rosette formation may be absent in the completely undifferentiated primitive cell tumors. The larger the number and the more distinct the rosettes, the more differentiated the tumor for they represent the beginning formation of the more mature ganglion cells. The histologic preparation of the tumor in this child showed a combination of sympathogonia and sympathoblasts with a few clusters but not well defined rosette formations indicating a high degree of malignancy (Fig. 5).

No elaborate classification of terminology is needed if we simply designate all the malignant primitive cell tumors as sympathicoblastomata of varying degrees of differentiation. This does away with a number of confusing names which attempt to label accurately the degrees of maturity of the constituent embryonal cells such as sympathogonioma, neuroblastoma gangliocellulare, et cetera.

The term sympathicoblastoma as suggested by Bailey and Cushing[1] is used in preference to neuroblastoma because the sympathoblast is pluripotential and not strictly a neuroblast but may develop into chromaffin cells. It also serves to distinguish these tumors from the medulloblastoma or neuroblastoma of the central nervous system.

TREATMENT

In a review of the reported cases one is impressed by the absence of discussion as to treatment probably because most of them are autopsy reports and deal largely with the pathologic features.

Mont Reid,[9] in 1930, stated that the reports showed that only one patient with a neuroblastoma had been successfully operated upon (Lehman,[8] 1917), and that irradiation had no appreciable effect.

Blacklock,[2] in 1934, stated that these tumors are the most malignant observed either in children or adults, metastases being frequent and extensive. Sympathicoblastomata were present in seventeen of his eighteen patients with sympathetic nervous system tumors and arose in the adrenal medulla in sixteen patients, in the superior cervical ganglion in one and in the celiac plexus in one. There was a 100 per cent mortality and the average duration from the onset of the clinical symptoms until death was nine weeks.

Meredith Campbell[3] reviewed twenty cases in which the mortality

was 100 per cent. The more recent reports of Scott and Palmer[10] and of Chandler and Norcross[4] confirm the high degree of malignancy of the extra-adrenal tumors as well as the adrenal.

However, we are forced to modify this almost hopeless prognosis since the reports of Farber[7] from the Children's Hospital in Boston in 1940. In his series, ten of the forty children with sympathicoblastoma, many of which were extra-adrenal, were alive and well from three to five years after the operative discovery of the tumor.

One is impressed by the unexpected results of the same treatment in one patient which has completely failed in another. Surgical removal followed by irradiation may fail in a patient with a tumor that has not metastasized, yet be successful in another patient with demonstrable metastases. The tumor may undergo spontaneous hemorrhage and necrosis and disappear without any treatment other than biopsy. It may undergo spontaneous maturation and develop into a benign ganglioneuroma comparable to the maturation which takes place in the development of the sympathetic nervous system.

This remarkable change was first observed by Cushing and Wohlback[5] and reported in 1927, although the possibility had been previously suggested by Dunn.[6] In Cushing's case a paravertebral swelling at the sixth thoracic level in a child two years old was explored and found to be a cellular sympathicoblastoma. It had extended into the spinal canal as well as the spinal muscles. It was mistaken for a sarcoma and subsided after Coley's toxins were given. Ten years later owing to the persistence of a paraplegia, an exploratory laminectomy was performed. This disclosed a relic of the former growth whose cells had become completely differentiated into a benign ganglioneuroma. A review at that time of the first section proved the original tumor to be a malignant sympathicoblastoma. Ober, in discussion,[4] mentions two patients in whom a similar change took place.

Farber[7] recommends the surgical removal of these tumors as soon as they are discovered, followed by irradiation. This may be successful even after local metastasis has occurred. He emphasizes, however, the importance of surgical removal as completely as possible first and the dangers of delay incident to pre-operative irradiation.

SUMMARY

A large malignant sympathicoblastoma arising in the sacral region in a child three weeks old was partially removed at operation. The remainder disappeared after two months of x-ray treatments and the child is alive and well four years later. This result supports Farber's[7] contention that the outlook in these cases is not entirely hopeless and that when a sympathicoblastoma is discovered treatment should be carried out even if the tumor cannot be completely removed.

Although these tumors rarely present a problem in urologic practice except in their differential diagnosis from embryomas of the kidney, the possibility of their extra-adrenal origin must not be forgotten.

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ADENOCARCINOMA OF THE URINARY BLADDER

THREE INSTRUCTIVE CASES

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Adenocarcinoma of the urinary bladder is a rare tumor. During the past ten years at Cook County Hospital there is a record of 531 urinary bladder tumors; of these, only two have been classified as primary adenocarcinoma. Scholl reported five instances in a review of 320 patients; G. G. Smith recorded one instance among 150 patients; Watson two in 653 vesical neoplasms; Geraghty one in 145; Motz three in eighty-seven. The incidence of glandular tumors in the Registry for Tumors of the Bladder of the American Urological Association in 1.8 per cent.

No one theory explains the etiology of glandular neoplasms of the urinary bladder. Those glandular tumors which occur in the urachal region are best explained by the theory of embryonal inclusions of urachal remnants. Portions of its epithelium, which fail to degenerate, may form cystic glandular structures which may undergo malignant transformation to adenocarcinoma of the fundus of the urinary bladder.

The etiology of glandular tumors in other portions of the bladder can be explained by Brunn's theory. He believed that invaginations of the bladder mucosa due to inflammation or irritation became pinched off to form small cysts, which condition we know as cystitis cystica. These cysts may become solid glandular structures and give rise to the condition known as cystitis glandularis. These glandular areas may undergo malignant transformation and give rise to adenocarcinoma of the bladder especially in the region of the trigone and bladder neck.

One cannot overlook the fact that tubular glands are regularly found in the bladder mucosa over the trigone and around the internal urethral orifice. The glands around the internal urethral orifice have been interpreted either as paraurethral glands or aberrant prostatic glandular tissue. In either instance, malignant changes could take place in these glandular areas.

Metaplasia has been used to explain the origin of the cell nests of Brunn, cystitis cystica, cystitis glandularis and adenocarcinoma of the bladder. It has been proposed that as a result of inflammation, regeneration or tumor growth, that the newly forming cells undergo a de-differentiation or reversionary process in the direction of the primary embryonal or blastomere cell, and as further growth goes on there is a re-differentiation to form a type of cell not identical with the original type. This new differentiation produces cells of a lower order of specialization than the original, but may occasionally progress higher to produce progressive metaplasia. It has also been pointed out that the columnar epithelium in the bladder may develop by means of indirect metaplasia; the dominant cell type of a tissue may become inferior to the recessive cell type which, in turn, becomes dominant. Thus, the transitional cell epithelium, which is dominant in the bladder, may by irritation become atypical and revert to an inferior recessive type, while the inert inferior recessive cylindrical cell becomes dominant. This could explain the development of a colloid carcinoma of the urinary bladder.

It is very evident, from a review of the literature, that many workers suspect a relation between cystitis cystica or cystitis glandularis and the development of adenocarcinoma of the bladder. Urologists can testify as to the rather frequent occurrence of cystitis cystica but they have not recorded their follow-up observations on patients with cystitis cystica over long periods of time. We believe cystitis cystica may be a very important lesion and that we should all concern ourselves with what happens to these lesions. By such a point of view we may be able to learn something about the development of urinary bladder new growths.

It is difficult sometimes to decide whether an adenocarcinoma of the urinary bladder is primary or secondary. For example, carcinoma of the prostate gland may involve the bladder in the trigone region and a differential diagnosis is often confusing. The uterus and rectum may also furnish a primary source of invading bladder tumors. It is not uncommon to have the pathologist report that operative bladder specimens of new growth contain typical areas of mucin secreting glandular tissue which he believes to have probably originated from some portion of the bowel. One must learn to interpret these areas as metaplastic glandular areas in a tumor whose structure is chiefly that of a transitional cell. However, careful

bowel study can be made to exclude the presence of a juxta-vesical bowel new growth. As a rule, secondary and invading tumors of the bladder are fungating and hard. Very rarely a primary glandular tumor of the seminal vesicles will invade the bladder in the region of the trigone. Primary glandular ureteral tumors may involve the bladder occasionally but their concomitant signs of obstructive uropathy will lead one to suspect their presence.

With the above facts in mind we wish to present the clinical data and findings of three patients who had adenocarcinoma of the urinary bladder and which we believe are unusually instructive.

Case 1.—R. E., female, white, single, fifty-six years old, was admitted to the Cook County Hospital November 22, 1938. She complained of marked frequency and burning on urination, both of which complaints had been more or less present for the past twenty years. The urethral pain and discomfort had been almost constant during these years.

In 1925 a cystoscopic examination of this patient by one of us (H. C.) disclosed a typical area of interstitial cystitis near the air bubble; he fulgurated the region lightly. The symptoms were partially relieved and seemed to almost disappear. Eleven months ago she experienced a sudden severe, relatively painless hematuria. A cystoscopic examination was done by her family physician, in another state, who informed her that she had a papilloma of the bladder. He removed tissue for a biopsy study and fulgurated the lesion. The pathologic study of the removed tissue revealed no definite new growth. No further treatment was instituted and there has been no further hematuria. In May, 1938, she again began to have a marked frequency and burning of urination; she also noted upper left lumbar backache. This discomfort was located by the patient in the region of the left kidney. All of these symptoms have persisted.

In August, 1938, another cystoscopic examination was performed and a circular area was found near the dome of the bladder, one centimeter in diameter, slightly elevated and flat, in the same area as the previously recognized and treated interstitial cystitis. There was no change in the muscosa over this area. However, the mucosa cracked and bled when the bladder was distended. The area was thoroughly fulgurated. There were no visible new growths in the bladder at this time.

Another cystoscopic examination was done on November 23, 1938, under nitrous oxide anesthesia. In the region of the previous interstitial cystitis there was a slightly elevated lesion, 1.5 centimeters in diameter; the mucosa over this lesion was rough, velvety and red, but not ulcerated. Three pieces from different areas of the lesion were removed by cystoscopic forceps for biopsy study and the lesion was

fulgurated. The pathologic report stated there was much necrotic tissue present infiltrated with red and white cells. In one area, there were several small nests of epithelial cells with large hyperchromatic, slightly irregular nuclei; some of these cells were isolated in the necrotic tissue. Intravenous urography revealed a normal upper urinary tract.

Diagnosis: Infiltrating carcinoma of the urinary bladder (Fig. 1).

The patient was re-admitted to the hospital, October 16, 1939. Her

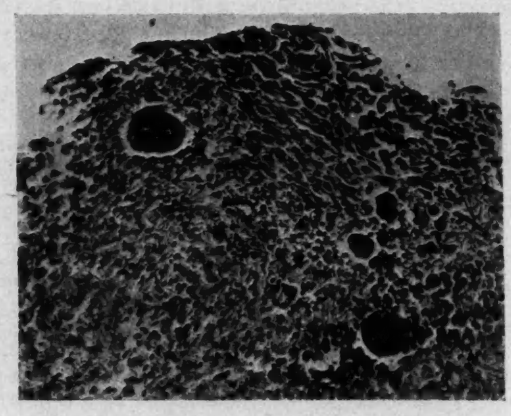

Fig. 1. Photomicrograph of biopsy tissue. This shows early infiltrating carcinoma of the bladder.

symptoms were the same. Cystoscopic examination revealed the character of the bladder lesion to be about the same. Since the previous biopsy study had revealed irregularly growing nests of epithelial cells and since there had been no therapeutic response to electrocoagulation, a segmental resection of the tumor-bearing area of the bladder was advised. X-ray studies of the lungs, pelvic and large bones, revealed no metastases. A barium enema of the colon revealed no bowel lesions. Bimanual examination of the pelvic organs was essentially negative. The electrocardiographic tracing was within normal limits. Urinanalysis was negative. The systolic blood pressure was 140, the diastolic 90. The blood chemistry was: non-protein nitrogen, 29 mgm. per cent; creatinine, 1.3 mgm. per cent; and sugar, 83 mgm. per cent. Blood studies showed 67 per cent hemoglobin, 3,680,000 red cells and 9,750 white cells. The differential count was normal.

A blood transfusion of 500 c.c. was done on October 17, 1939. The next day, a wide, segmental resection of the involved area of the bladder was done under ether and nitrous oxide anesthesia. The patient made an uneventful immediate postoperative recovery, except for a

phlebitis and swelling of the entire left lower extremity. The suprapubic fistula was slow in healing; so, a fistulectomy and secondary closure of the bladder was done on December 13, 1939, and the suprapubic wound healed promptly.

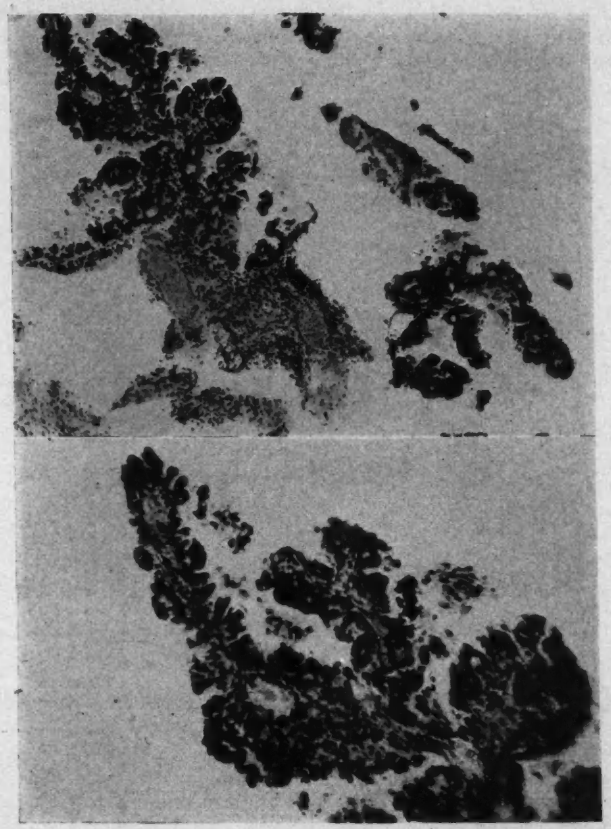

Fig. 2. Photomicrograph of section of surgical specimen. This shows an adenocarcinoma of the bladder.

The pathologic report of the removed bladder tissue was as follows: The surgical specimen was 6 by 3.5 by 1.5 cm. (in dimensions) and was purplish-gray and firm. The surface was covered by small, nodular elevations. There was a linear depression in the midline, which

had a darker purplish-red color. On sections made through the nodular elevations, the tissue was grayish-white in color. Microscopic study revealed that the mucous membrane of the tumor-bearing area was missing and the underlying tissue was very edematous, vascular and heavily infiltrated by round cells. In one area at the surface, there was a papillary-like structure lined by a cuboidal type of epithelium, which formed suggestive small acinic structures. The lymphatics just beneath this small polypoid mass were occluded by nests of tumor

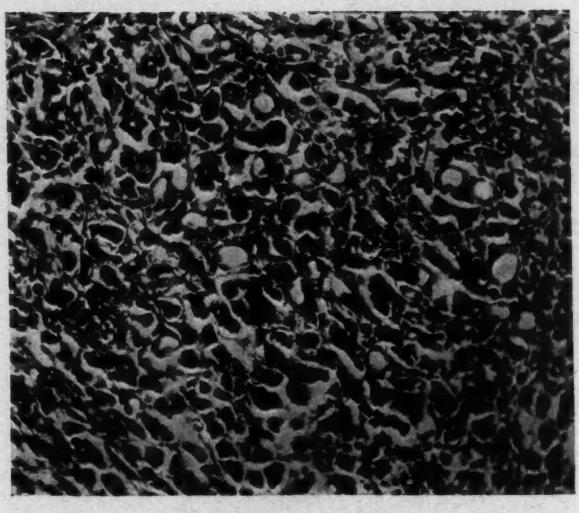

Fig. 3. Photomicrograph of section of lymph node. This shows metastatic adenocarcinoma.

cells. The tissue of the muscular layer of the bladder was edematous and contained focal accumulations of round cells (Fig. 2).

Diagnosis: Adenocarcinoma of the urinary bladder.

On February 18, 1940, cystoscopic examination revealed a normal bladder. Its tolerance to capacity was slightly diminished. The patient entered the hospital again, March 3, 1941. She had gained weight and felt fine, but her bladder was still irritable. The urine contained no pathologic elements. During the last two weeks the left leg had become swollen and edematous. Physical examination revealed a pitting edema of the lower left leg and a marked increase in the size of the left thigh. There was also a group of hard, rather fixed, lymph glands over the left inguinal region. There was a tender area over the appendiceal region but palpation revealed no mass. A barium enema at this time

furnished no information. Cystoscopic examination again revealed a normal bladder, except for a slightly reduced capacity.

On March 5, 1941, an inguinal gland was removed for pathologic study. This revealed the structure of the lymph node to be completely replaced by solid nests and cords of irregular tumor cells, with hyperchromatic, irregular nuclei, and occasional atypical mitotic figures. These cords appeared to be separated by moderately dense connective tissue structures. In the periphery, the lymphatic sinusoids were oc-

Fig. 4. Photomicrograph of section of skin biopsy. This shows metastatic adenocarcinoma.

cluded by nests of tumor cells which appeared edematous. There were scattered islands of lymphocytic cells.

Diagnosis: Metastasis of a low columnar cell carcinoma into the inguinal lymph nodes (Fig. 3).

The patient received deep x-ray therapy from March 13, 1941, to April 9, 1941, under the following conditions: 800 kilovolts, 10 milliamperes, 1 lead, 1.56 tin, 2.62 copper, 3 aluminum, field 20 by 20 cm.; 70 cm. focal skin distance, 250 roentgen units, 7.5 minutes; ten treatments were given to the anterior and ten to the posterior lower left abdominal quadrant and suprapubic regions.

The patient was admitted to the hospital again June 10, 1941, with what appeared to be an exquisitely painful and tender skin reaction from x-ray treatment over the left hip, medial and anterior aspects of

the left thigh. The pain of this reaction was so severe that the patient could not sleep. There was also swelling of the left thigh and pitting edema of the left lower extremity.

On June 17, 1941, a biopsy study of the above mentioned skin revealed an infiltration carcinoma; in places, the tumor cells appeared to form glandular structures.

Diagnosis: Metastatic adenocarcinoma of the skin (Fig. 4).

On July 4, 1941, the patient became septic and had chills and fever.

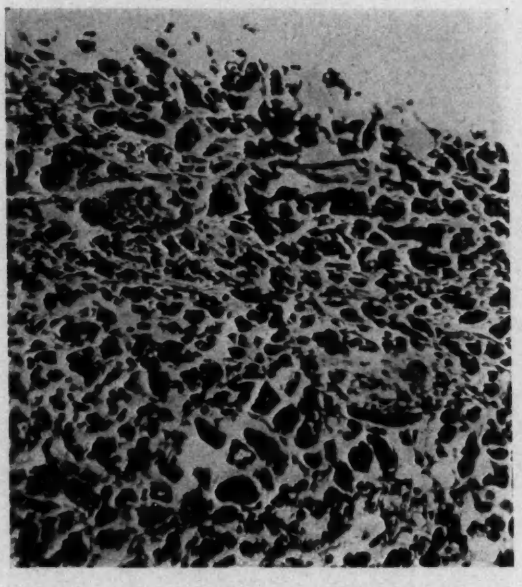

Fig. 5. Photomicrograph of section of postmortem bladder. This shows closely packed tumor cells up to inner surface of bladder. There is absence of the mucosal layer of bladder.

The urine, which had been clear and uninfected, now contained much pus and many bacilli. There was marked tenderness over each renal area. Conservative therapy and sedation were ordered. The clinical picture of urosepsis became quickly exaggerated to cause death on July 7, 1941.

Autopsy was permitted to obtain the urinary tract and examine the remainder of the viscera of the abdomen and chest through an abdominal incision.

Diagnosis: Primary adenocarcinoma of the urinary bladder with metastases to lymph nodes, skin, lower thirds of uterus, entire peritoneal surface and rectal wall.

Case 2.—P. S., white, male, sixty-seven years old, was admitted to the Cook County Hospital, January 31, 1942. The admission diagnosis was "infected vesico-cutaneous fistula." He had had a right nephrectomy for a pyonephrosis, four years ago. Since that time he had enjoyed good health. About October 1, 1941, he noted a gradual swelling of the suprapubic region; this became very painful and tender. The swelling ruptured and drained much pus. This lesion healed except for one small opening from which the patient believes that urine drained. A few weeks later, this same area became hardened, indurated and began to swell again. The draining area became larger and the surrounding tissues began to break down. The patient now noted a

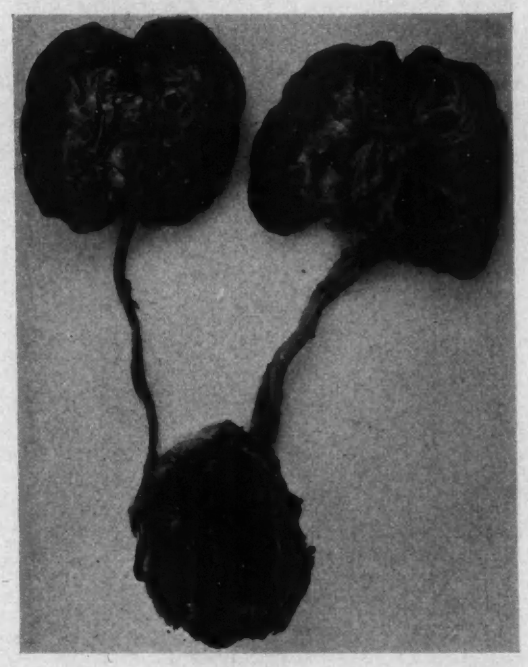

Fig. 6. A photograph of the urinary tract obtained at necropsy, patient No. 1.

frequency of urination and his urine was cloudy. His appetite and weight had not changed appreciably.

Physical examination revealed a white man, fairly well developed and nourished, and not acutely ill. His blood pressure was 138 systolic and 80 diastolic, pulse, 96; respirations, 24. There was a right lumbar scar with herniation. Over the suprapublic region there was a large necrotic, elevated, hard, bizarre-colored, foul smelling mass, with rolled edges. This lesion was 15 by 15 cm. and protruded 7 or 8 cm. above

Fig. 7. Photograph of anterior abdominal wall. This shows perforation of suprapubic region by a bladder tumor.

the level of the anterior abdominal wall. The remainder of the physical examination was without significance (Fig. 7).

Cystoscopic examination revealed a large fungating carcinoma in the fundus and the dome of the bladder; irrigating fluid escaped from the suprapubic mass. It seemed to the cystoscopist that a bladder tumor had extended through the anterior abdominal wall. Tissue was removed from the bladder for pathologic study. These tissues showed many glandular structures which were lined by cells with hyperchromatic irregularly shaped nuclei. There were also many connective tissue stalks from which papillary projections were seen; these projections

were also lined with hyperchromatic cells. There was much necrotic material and many polymorphonuclear cells in the tissues.

Diagnosis: Papillary adenocarcinoma of the urinary bladder (Fig. 8).

Biopsy studies of tissue removed from the suprapubic mass revealed the same type of tumor (Fig. 9).

Sigmoidoscopy showed the rectum and sigmoid to be normal as far

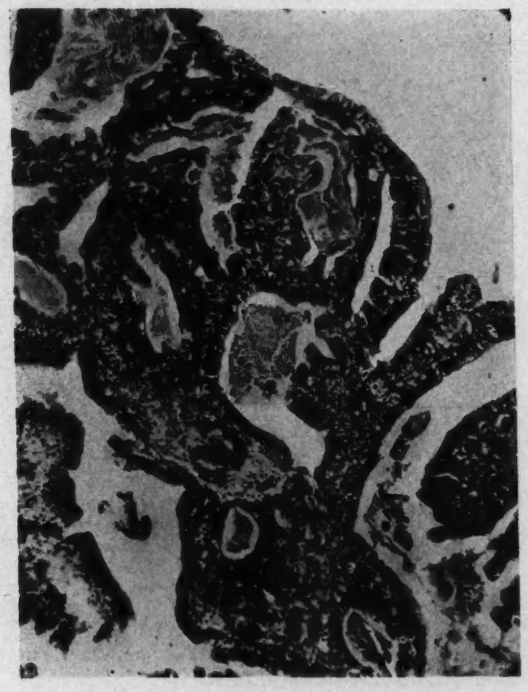

Fig. 8. Photomicrograph of section of biopsy tissue of bladder tumor, bladder side, patient No. 2. This shows adenocarcinoma.

up as 25 cm. A barium meal and a barium enema revealed no pathologic lesion in the stomach or large bowel. The electrocardiographic tracing was within normal limits. The blood chemistry was normal. An x-ray study of the chest revealed healed tuberculosis. The Wassermann and Kahn reactions of the blood were negative.

This patient is still alive. A necropsy report has been anticipated.

Case 3.—M. E. G., white, female, married, aged forty-five, was admitted to St. Luke's Hospital, December 9, 1938. She had experienced a painless hematuria for over a year; her bladder had become irritable during the past four months.

Her past history was not important. Her weight had not changed and the appetite had remained good. She had not menstruated during the past year.

The physical examination revealed a well-nourished female. The

Fig. 9. Photomicrograph of section of biopsy tissue of suprapubic tumor.

blood pressure was 140 systolic and 100 diastolic. There was no tenderness over the bladder or renal areas.

There was an indurated irregular tangerine sized mass which occupied the area of the left Bartholin gland; there was no inflammatory reaction over this mass and it was movable.

A bimanual examination revealed a midline mass about 1 inch in diameter over the fundus of the uterus.

The urine was grossly bloody but not infected. The blood examination revealed 4,130,000 red cells, 7,100 white cells and 12 gm. per cent of hemoglobin. The differential count was normal. The blood chemistry findings were: 7.9 mgm. per cent of urea nitrogen, 26 mgm. per cent of total non-protein nitrogen and 97 mgm. per cent of

sugar. The bleeding and coagulation times of the blood were within normal limits. The two-hour intravenous phenolsulphonphthalein test was done after twenty-four hours of bed rest and a cessation of hematuria to yield 80 per cent.

A plain x-ray study of the urinary tract revealed the kidneys to be of normal size, contour and in their normal positions. There was no evidence of urinary calculi. There were no bony changes. A cystogram revealed a large bladder and no filling defect.

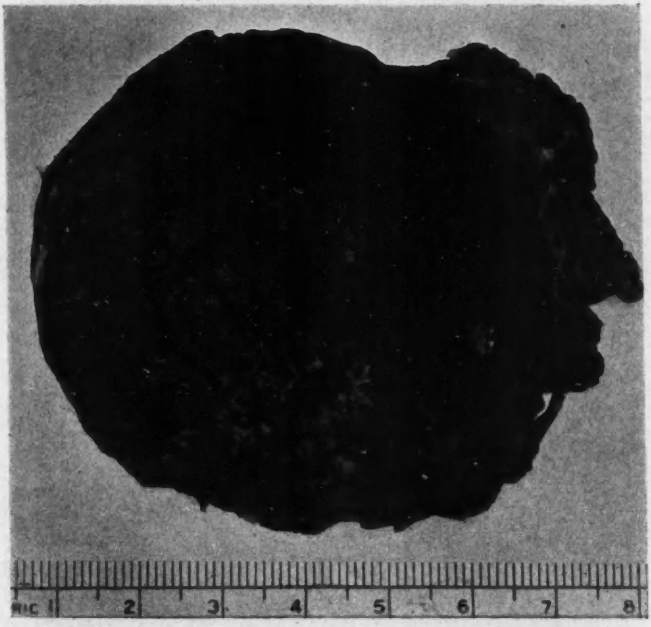

Fig. 10. Photograph of vesical tumor removed from patient No. 3.

Cystoscopic examination on December 9, 1938 revealed the bladder urine to be grossly bloody. The bladder capacity was 16 ounces. There was a sessile ulcerating mass about 1.5 inches in diameter in the midline of the anterior bladder wall, two inches or more from the vesical neck. The remainder of the bladder was normal.

On December 13, 1938, under ether anesthesia, a wide segmental resection of the tumor bearing area of the bladder was done. The tumor was located more in the fundus than in the anterior wall of the bladder. An elliptical incision was made over the mass in the region of the left

Bartholin gland, a definite line of cleavage was found and a well encapsulated mass was removed. The patient made an uneventful postoperative recovery and was discharged from the hospital January 5, 1939.

Fig. 11. Photomicrograph of section of tumor removed from bladder of patient No. 3. This shows colloid carcinoma of the urinary bladder.

The pathologic report on the tissue which was removed from the bladder was as follows: This disc of tissue was 8 by 7 cm. in diameter and it ranged in thickness near the center to about 3 cm. (Fig. 10). On the lining side, there was a sessile granular red sur-

face 6 cm. in diameter and around this was hyperemic mucosa ranging from 0 to 20 mm. The opposite side was an uneven, somewhat nodular surface. Tissues exposed near this side contained gray opaque gelatinous material with yellow streaks. Histologically, the tissue had narrow fibrous septums that extended between large masses of mucinous or pseudomucinous material (Fig. 11). Some of the fibrous septums had exudates of lymphocytes and plasma cells, and a growth of fibroblastic tissues. Near a few of these sep-

Fig. 12. Photograph of perineal tumor removed from patient No. 3.

tums in the pseudomucinous material were a few small groups of epithelial cells. They were cuboidal or low columnar and had vaguely some lumen-like structures. Most of the material, however, was pseudomucinous. In some areas there was a large amount of pseudomucin and a few small groups of epithelial cells. Wherever these epithelial cells extended into the stroma, they were associated with mucin or pseudomucinous material.

The tissue removed from the region of the left bartholin gland was described as a hard irregular mass 4.5 by 4.5 by 2.5 cm. (Fig. 12). It had almost the consistency of cartilage and on surfaces made by cutting there was gray gelatinous material and some yellow. Histologically, it was described as similar to the histologic preparations of the bladder tumor (Fig. 13).

Diagnosis: Colloid carcinoma of the urinary bladder; metastatic carcinoma of the perineal tissues.

This patient was examined August 17, 1939. General physical

examination revealed nothing of significance. Her bladder urine contained B. proteus by culture. A cystoscopic examination showed the bladder to be grossly normal. Sulfathiazole by mouth eradicated the B. proteus.

Fig. 13. Photomicrograph of section of perineal tumor removed from patient No. 3. This shows colloid adenocarcinoma.

General and cystoscopic examinations have been made on this patient February 22, 1940, September 19, 1940, March 27, 1941, and October 10, 1941, and revealed the patient and her bladder to be normal. She has no complaints and feels well.

DISCUSSION

In the first patient, we have an instance of interstitial cystitis, which, after fifteen years, developed into a carcinoma of the bladder. This is a rare occurence. Similar instances have been reported.

Although the new growth was located near the urachal region, we believe the glandular structures of this tumor were brought about by metaplasia. In the first biopsy studies, pathologists were not impressed by the glandular character of the tumor; they were more impressed by the infiltrative nests of irregularly growing cells throughout the thickness of the bladder wall. All later tissue studies showed the tumor to be glandular in structure.

Another interesting feature of the pathologic condition in this patient is the metastases of bladder tumor cells not only to the deep lymphatics but also to the superficial set of inguinal lymph nodes. The superficial inguinal lymph nodes are not commonly involved by bladder tumors.

The metastases of this tumor to the skin stimulates discussion of the relationship of deep x-ray therapy to this phenomenon. Skin metastases of uterine or ovarian new growths have been noted by gynecologists in instances in which deep x-ray therapy has been used. One could believe that deep x-ray therapy would obliterate lymphatics rather than open them up to metastasizing tumor cells. In an effort to explain the migration of tumor cells to the superficial lymphatics and skin, one must keep in mind that it may be possible to use too much *deep* x-ray therapy.

It should be noted that the interior of this bladder, following segmental resection of the tumor bearing area, was normal at all times by cystoscopic observation. However, the bladder irritability and slightly lessened capacity persisted.

Finally, the series of pathologic pictures which this bladder tumor has presented again emphasizes the already known fact that tumors in the dome and fundus of the bladder have malicious metastasizing character, and use this power of migration at an early date.

The etiology of the bladder tumor in the second patient could easily be explained by the urachal embryonic rest theory. The location of the tumor and its glandular character favor this presumption. We believe our clinical studies have excluded other possible primary sources of this tumor.

The principal reason for including this patient in this report was

the spontaneous growth of the tumor through the abdominal wall. This is a rare occurrence. This extension through the anterior abdominal wall was apparently preceded by a perivesical abscess which finally ruptured spontaneously.

The third patient had a colloid carcinoma of the urinary bladder with extension of the tumor to the region of the left Bartholin gland. We do not have an explanation of this metastasis. The patient is now living in her fourth postoperative year. The etiology of her vesical tumor could be explained by the theory of indirect metaplasia, whereby the inert recessive columnar cell of the bladder becomes dominant.

SUMMARY

Three instances of adenocarcinoma of the urinary bladder have been reported.

Two of these tumors probably owe their origin to metaplasia; one to direct metaplasia and the other to indirect metaplasia.

The relationship of cystitis cystica and cystitis glandularis to the origin of adenocarcinoma of the urinary bladder is emphasized.

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DISCUSSION

DR. ALEXANDER RANDALL (Philadelphia, Pa.): May I ask a question? It is always pitiful to me how long one sometimes has to wait to get an answer, because it is certainly eighteen years or more ago that I saw the son of a friend of mine who was a little boy of six years of age, with what we thought was a renal tumor. I explored his left renal region, found that the tumor was totally unassociated with the kidney, which appeared normal, and going downward uncovered a perfectly unrecognizable mass. To me, at operation, it appeared more like the back of a placenta than anything else. It was definitely retroperitoneal. I foolishly took a biopsy only to run into very drastic hemorrhage. I felt myself lucky to pack the region with iodoform gauze and oversew it with mattress sutures and to have the boy recover.

Now, it was not until today that I recognized the diagnosis when I saw these sections on the screen. At the time, it was discussed among a number of pathologists without a diagnosis being made. The vascularity made me feel it was a hemangioma and yet it did not appear microscopically as a hemangioma. The child was started on intensive irradiation until Dr. Pancoast called a halt. The child had received as much as he thought it was safe to do. But I persuaded him that the child was going to be dead if he did not persist. The child's only chance was to give a maximum and then some, perhaps, of irradiation, and to do everything we could to preserve the skin. Without being able at all to recall the amount of irradiation he got by x-ray, we nevertheless gave him a maximum dosage. The bronzing of his skin persisted for years and years, but his tumor disappeared. He was back at school, playing baseball, apparently a pretty husky sort of kid. His father is rather lean, and he took after his father; but he was a perfectly healthy boy.

Years went by and we were all quite glad that we had gotten the boy out of a very bad ditch. He must have been around twelve or thirteen years of age, at his father's camp, when he took a natural belly-whopper in swimming, immediately had a pain and subsequently developed a mass in his lower left quadrant. He had a moderate amount of obstipation from it and came back home, not

sick, but a bit crippled. It was easy then to palpate a large ovoid mass way low down in the left quadrant.

Having done such a poor operation before and being very close to the parents, I was delighted to assist a general surgeon in exploring the abdomen intraperitoneally. A mass about the size of a croquet ball, which seemed large in a slim child, chiefly encapsulated, was boldly incised by this general surgeon, while my knees were knocking together, and he opened into a cyst. The evident catastrophe had been hemorrhage, and he evacuated a large quantity of old blood clot. Upon opening it, nothing was found except a heavy capsule, and deep down in it a nubbin of tissue. The general surgeon enucleated it with his finger nail. It didn't bleed. The boy seemed all right. The tissue was subsequently examined and found to be exactly the same as the previous tumor of some six or seven years before. We backed out again, feeling quite comfortable about the situation.

Again, a period of years went by, this time without any reason to give further x-ray, and the boy died supposedly of metastasis to the liver. I have often wondered whether that is within the habit of these tumors. The lesion of the liver was not explored. There was not an autopsy. That he had every evidence of hepatic neoplasm and died from it is the written record today.

DR. GEORGE F. CAHILL (New York, N. Y.): I wish to congratulate Dr. Hepler on his scholarly discussion of medullary adrenal tumors and the report of a most extraordinary and successful result in the treatment of one in an unusual situation.

These tumors are not as infrequent as has been reported. We have just discharged from the hospital a four-year-old child after successful removal of one of these tumors. We have another child two months old with a similar condition. The dissemination of these tumors has been described by Dr. Pepper and Dr. Hutchinson. The Boston surgeons are to be congratulated for insisting that these tumors can be corrected surgically and we concur in this. Our cases have not shown the sensitivity to x-ray that Dr. Hepler has shown in his case.

DR. ALEXANDER B. HEPLER (Seattle, Wash.): Dr. Cahill has answered Dr. Randall's question concerning metastases and has

brought up the interesting question of treatment. The unpredictability of results justifies every effort towards a cure regardless of whether or not metastases are present. Sometimes these tumors disappear spontaneously or may go on to maturation to a benign tumor.

There are only two things to do: (1) immediate removal of the tumor or as much of it as possible and (2) postoperative irradiation. Although there may be many failures, the occasional unexpected results such as the response of the remnant of the tumor in this child to x-ray treatment warrants the effort.

THIRD DAY MAY 29, 1942

THE RENAL LESIONS IN VON HIPPEL-LINDAU'S DISEASE

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and DuPONT GUERRY, III, M.D.
New York City

Angiomatosis retinæ was first described by von Hippel in 1895. Hemangioblastomas were reported by various observers to occur associated with other lesions of the central nervous system. Lindau was the first to recognize that a generalized form of hemangioblastoma occurred, associated not only with tumors of the retina, but with cysts of various visceræ, cystadenoma of the pancreas and with hypernephroma of the kidney. Subsequent investigators have shown that lesions may occur in many visceræ, including syringomyelia of the cord, cysts of the dura and of the pia arachnoid, cysts of the omentum, mesocolon, kidney and pancreas and death is apt to occur following the lesions in the cerebellum and medulla oblongata. It has been also shown that the disease may be familial or start early in life.

Next to the retinal changes which apparently occur in all cases according to Lindau, one of the more common findings of the disease has been cyst of the pancreas. Such cysts have been removed surgically as in the case reported by Davison, Brock and Dyke. Hypernephroma is supposed to occur less frequently than the pancreatic cysts. Lindau reported that it was present in six out of his fifteen cases and since it occurred in the case of Davidson, et al., and in that of Wolf and Wilens and also in the case we are reporting, the proportion has been increased to nine in eighteen cases or 50 per cent.

The case which we report is of interest in that the patient showed the hormonal deficiency changes thought to be due to pituitary involvement. She had no demonstrable pancreatic cysts and her large renal tumor was recognized and removed and was a hemangioblastoma.

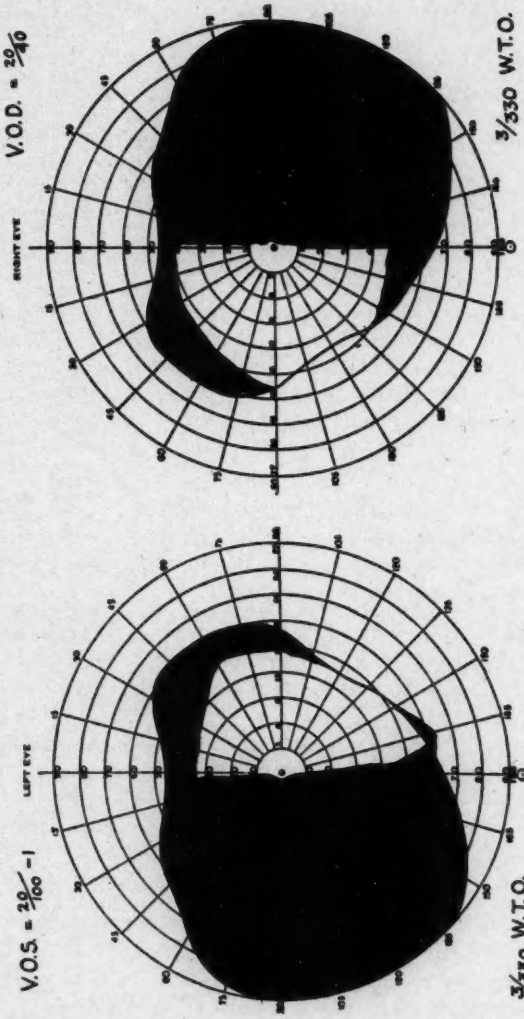

Fig. 1. The visual field, showing bitemporal hemianopsia (corridor vision).

REPORT OF CASE

V. K., a twenty-six-year-old white, unmarried woman was admitted to the Institute of Ophthalmology on January 11, 1942, with the complaint of failing vision for eighteen months.

Family history was essentially of no importance. All the immediate family were alive and well and there was no history of any familial pathologic condition.

Fig. 2. Radiograph of skull showing increased size of sella turcica, especially in its posterior portion.

Following a fall from a bicycle at the age of twelve, without loss of consciousness at that time, the patient has had gradual progressive bilateral deafness. At the same period she has had frequent but intermittent headaches. Her menses began at twelve years and were fairly regular for four years. They then became irregular with lessening of her menses for six or seven years and for the last five years she has not menstruated at all. There have been no urinary symptoms of any

character. At no time has hematuria occurred. For a number of months previous to admission she has had several attacks of dull right flank pain lasting for several days.

For eighteen months she has had impairment of vision so that she was able to see only directly in front of her and frequently ran into objects while walking. Because of this visual impairment she was referred to the Eye Institute.

Examination there disclosed that her eyes showed V.O.D. 20-40,

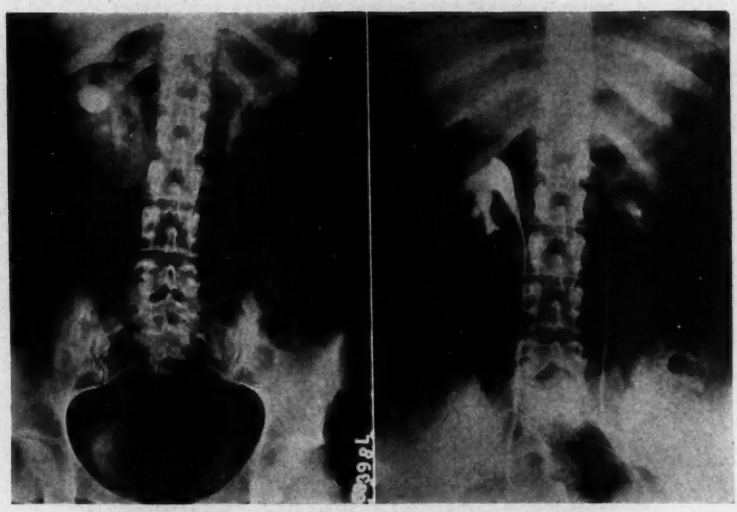

Fig. 3. *(left)* The intravenous urogram showing a distorted shadow of the right renal pelvis.

Fig. 4. *(right)* The retrograde urogram showing distortion of shadow suggestive of tumor of the right kidney.

V.O.S. 20-100-1. The muscle balance was normal except for impaired convergence (she had orthophoria for distance and exotropia). There was marked primary optic atrophy with extreme pallor of the discs. The visual fields showed a bitemporal hemianopsia (Fig. 1).

On general physical examination a mass was made out in the right flank. Radiograph of the skull (Fig. 2) showed a greatly enlarged sella turcica.

The patient was transferred to the Neurological Institute with the diagnosis of tumor of the pituitary and tumor of the right kidney. At the Neurological Institute, studies of the skull and the urinary tract by intravenous urograms (Fig. 3) caused her to be transferred

to the Squier Urological Clinic, with a diagnosis of right renal tumor and von Hippel-Lindau's syndrome.

Cystoscopy and retrograde pyelograms (Fig. 4) showed a deformity of the right renal shadow similar to that seen with renal tumor. There was no evidence of metastasis in radiographs of the lungs.

The patient spoke in a high flat voice. She was well nourished with a feminine figure with the exception of flat adolescent type male breasts. Her hair distribution was of a normal female. Her clitoris was

Fig. 5. A section showing central location of tumor with distortion and compression of kidney.

small, as was her uterus. The ovaries were neither palpable nor tender. The blood pressure was 136/75. Her glucose tolerance test was approximately normal.

She was operated upon and her abdomen first explored through a transverse right abdominal incision. There were no palpable cysts in intestines, pancreas, liver, spleen or left kidney. The large right renal mass was removed transperitoneally with the perinephritic fat attached, after first ligating and dividing the renal vessels.

Following operation she made an uneventful recovery and later was returned to the Neurological Institute for study of her pituitary-cerebral condition.

Pathologic Report: (Squier—No. 5506) Specimen: Kidney.

Gross Description: The specimen was a large kidney (measuring 15.0 cm. by 8.5 cm. by 4.0 cm.) and weighing 700 grams. There was

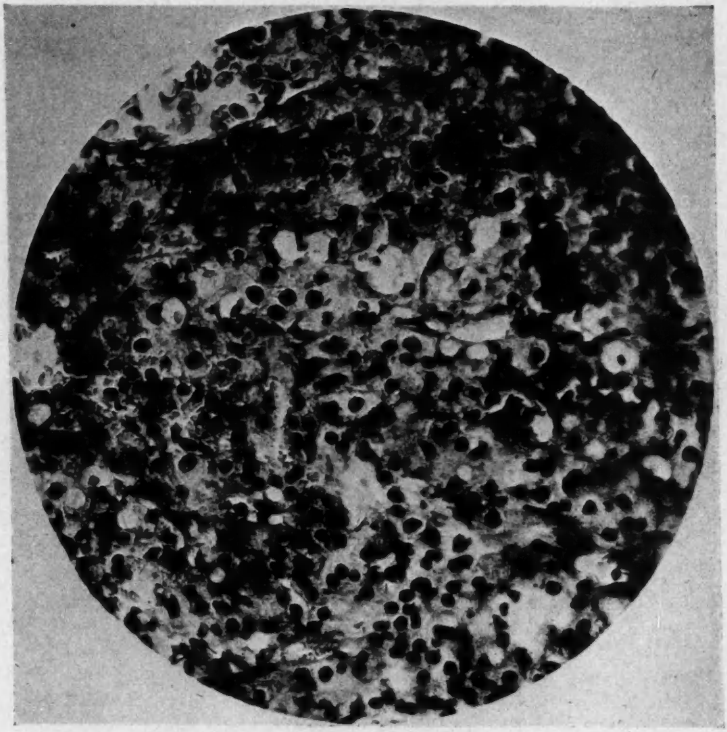

Fig. 6. A low-power field showing intertwining masses of small cells with small round nuclei.

a large, firm, nodular mass at the lower pole, grayish-red in color, extending upward to involve the lower half of the external surface, and measuring 10.0 cm. by 7.0 cm. Over this area the renal capsule stripped with some difficulty. The external surface of the upper half of the kidney including the upper pole was smooth and reddish-brown in color.

Over this area the capsule stripped with ease. On section (Fig. 5), the tumor mass was seen to have extended through to involve the entire lower half of the kidney substance, there being no normal renal tissue in this portion. The cut surface of the tumor was firm, smooth and purplish-gray in color. In the upper half, the tumor was centrally situated, causing marked compression of the renal pelvis and calyces.

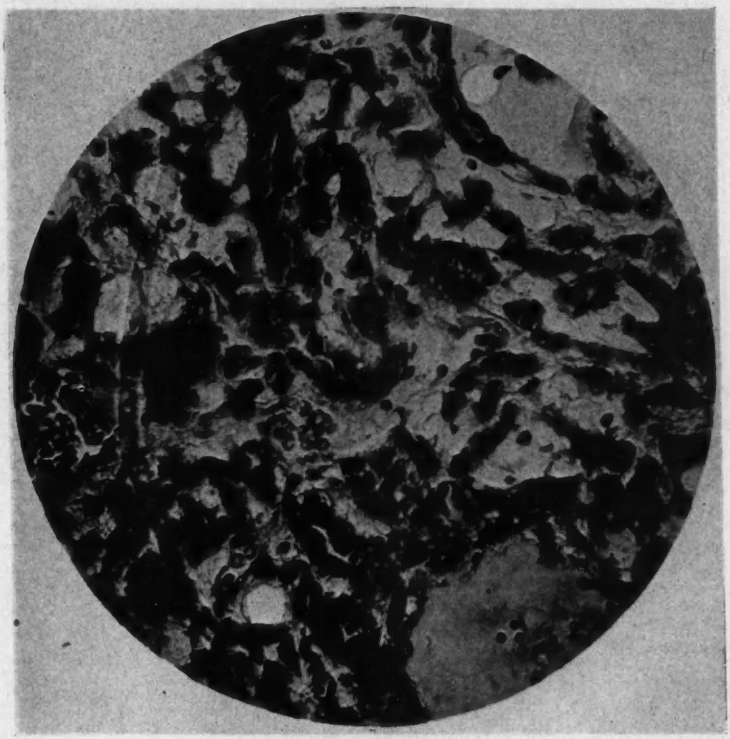

Fig. 7. A low-power field showing cells tending to form capillary spaces.

There was a small amount of normal renal tissue at the periphery in this region.

Microscopic Description: The sections presented somewhat different pictures in different areas. In some fields were seen a uniform array of intertwining masses of small cells with small round nuclei. They were closely crowded, showed no definite cell boundaries and lacked

any particular pattern (Fig. 6). In some other areas the cells were larger, possessed fairly large oval, pale nuclei and clear cytoplasm. In still other areas numerous lacunæ occurred. They were lined by a thin endothelium containing flat nuclei, and some were filled with blood. Small spaces resembling capillaries were frequently seen. Their lining

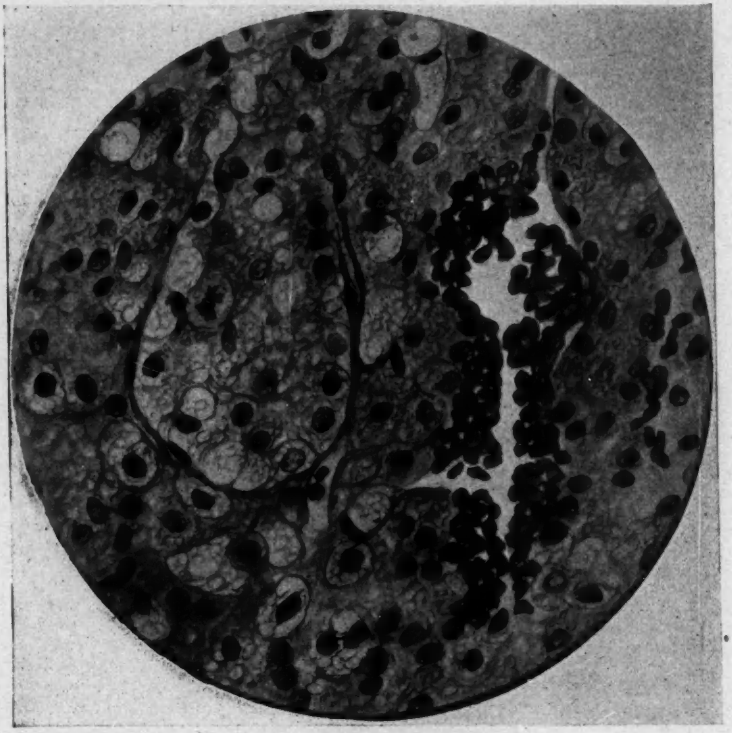

Fig. 8. A high-power field showing a cavernous area and nearby foam cells (xanthomatous).

cells contained larger, rounder nuclei which protruded into the lumen (Fig. 7). Between these "hemangiomatous" areas were broad sheets of large, pale, vacuolated "foam cells" with oval to round nuclei (Fig. 8). The exanthomatous cells contained coarse discrete flat globules when stained for fat (Fig. 9). Some large nuclei occurred (small giant cells of Lindau).

DISCUSSION

This is an unusual neoplasm of the kidney. It differs in many respects from the so-called hypernephroma or carcinoma of the kidney. In the first place there is a marked tendency towards

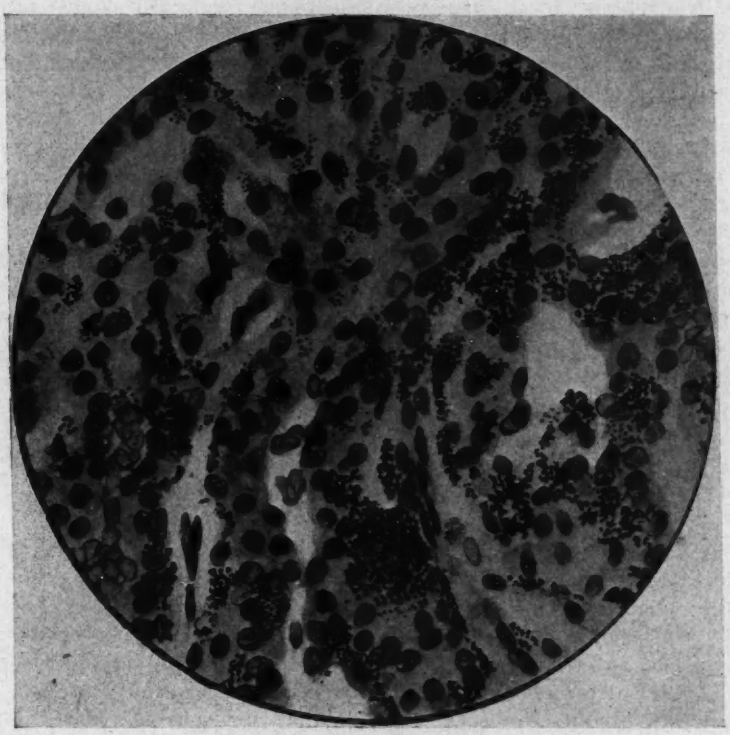

Fig. 9. A high-power field showing fat globules within the xanthoma cells.

formation of capillaries. Then again there is the frequent massing of "foam cells" between hemangiomatous areas. While xanthoma cells occur in other tumors and frequently in carcinoma of the kidney, they are usually seen within or near areas of hemorrhage and necrosis. Thus, they represent the phagocytic response of the

"resting wandering" endothelial cells, to the spilling of blood and fat into tissue spaces. In our case, however, the xanthoma cells are part of the architecture of the tumor, they constitute the interlacing pattern of cells in many fields and become foamy through their local activity.

Correlating these findings in the kidney with the clinical picture presented by the patient, one may conclude that we are dealing here with a case of Lindau's disease affecting the kidney. The pathologic findings resemble the cerebellar and retinal lesions as described by Lindau, Shapiro, Davidoff, Cushing and Bailey. They all agree as to the hemangiomatous character of the lesions both in the cerebellum and retina (von Hippel's disease). From the description of the microscopic sections of the tumor reported by Davison, Brock and Dyke, their tumor showed large pale, almost transparent cells in strands and in alveoli and numerous areas of hemorrhages and necrosis, all surrounded by a thick fibrous capsule and with numerous cysts in other renal areas. Our tumor seems to differ in this respect: instead of resembling the so-called hypernephroma as described by them, ours more resembled those lesions in the nervous system and retina as described by Lindau.

It was Lindau who first noted the heredofamilial character of the hemangiomatous cysts of the cerebellum and their frequent association with the angiomatosis of the retina, cysts of the pancreas and "adenoma" or "hypernephroma" of the kidney.

The origin of the hemangioblastomas seems to be considered to be congenital by most observers. Karlefors showed that in the third month of fetal life, a vascular mesenchyme is situated upon the posterior medullary velum. The cerebellar hemispheres also begin to develop at this time and, according to Lindau, part of the original vascular mesenchyme lying on the posterior medullary velum might be drawn into the cerebellar hemispheres. The midline position of these tumors is explained by the original position of the primitive vascular plate.

The presence of neoplasms in other organs can be explained upon the same basis. In the third month of fetal life vascularization of the retinæ and ingrowth of the mesodermal elements into the pancreas also occur. Contemporary vascular maldevelopment of the kidney may also explain the renal lesions and cysts. Lindau compares the disease in its resemblance to tuberous sclerosis,

von Recklinghausen's disease and other heredofamilial syndromes. Thus a genotypical origin is suggested and, if such be the case, one must surmise a disturbance affecting scattered capillaries of the vascular system. All lesions constituting the syndrome should have a common denominator. Thus in Lindau's syndrome, the cerebellar, retinal, visceral and (in our case) renal lesions are hemangiomatous in character.

The symptoms depend upon the structures involved; the failing vision is due to eye involvement, and blindness may follow. In our case the involvement of the pituitary interestingly was followed by atrophy of the breasts, dysmenorrhea and then amenorrhea, and atrophy of the uterus and ovaries. Our patient did not show on the exploration of the abdomen any of the customary lesions of the pancreas or other viscera, although surgical inspection is at times indefinite. The tumor of the right kidney, which was large enough to be palpated, was easily removed surgically.

SUMMARY

A case of von Hippel-Lindau's disease with retinal lesions, pituitary syndrome and right renal tumor. After diagnosis of the renal tumor, it was removed transperitoneally and microscopic study of the large tumor showed that the renal lesions were that of hemangioblastoma.

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MYELOCYTOMA OF THE KIDNEY

REPORT OF A CASE

HERMAN L. KRETSCHMER, M.D.

From the Presbyterian Hospital, Chicago, Illinois

I wish to report the following case because of the problem it presents in diagnosis and also because of its rarity from the urologist's point of view.

R. K., male, aged two and one-half years, referred by Drs. David M. Kane and John Sheldon, was admitted to the Presbyterian Hospital on March 24, 1940.

Seven weeks before admission to the hospital, the child had a cough which persisted for four days. Night sweats and fever had been present for four weeks. The temperature ranged from 99 to 100. During the past two weeks he had been weak and unable to walk, and the mother noticed some swelling under the eyes, enlargement of the abdomen and swelling of the feet.

Physical examination revealed a mass in the right upper quadrant that was smooth, hard, and not painful. It extended from under the arch of the ribs to the antero-superior spine and beyond the border of the right rectus muscle. The veins of the right chest were prominent.

The blood pressure was systolic, 108; diastolic, 80.

Urinalysis: Many specimens were examined with negative findings. Several examinations for the presence of Bence-Jones protein gave negative results.

Examination of the blood revealed the following:

Date	Reds	Whites	Hemoglobin	Polymorphs.	Lymphocytes	Eosinophiles	Basophiles
3/24/40	3,850,000	11,800	74%	49%	45%	2%	4%
3/25/40				54%	46%	0%	0%
4/ 3/40	4,450,000	10,800	85%				
4/ 9/40	4,650,000	10,400	92%	58%	36%	2%	4%

Roentgen-ray examination was negative for stone. Intravenous pyelogram disclosed that the pelvis of the right kidney was displaced upward and distorted—changes compatible with a tumor. The pelvis of the left kidney was enlarged and irregular. This raised the question of the possibility of a bilateral lesion. A bilateral Wilms' tumor and the possibility of polycystic disease were taken into consideration.

The presence of a palpable tumor on the right side, coupled with a filling defect, led to a tentative diagnosis of right renal tumor, probably Wilms'.

Roentgen-ray treatment was instituted; a total of 1200 r. The treat-

ments were daily for six days, and as a result there was a very rapid diminution in the size of the tumor. As a matter of fact, the rapid reduction was so striking that it led me to doubt the correctness of the diagnosis of Wilms' tumor, because I had never seen this type of tumor respond so rapidly to x-ray therapy.

Operation consisted of a right nephrectomy performed on April 1, 1940. A transfusion of 200 c.c. of whole blood was given following the operation. Convalescence was uneventful and the patient left the hospital on April 17, 1940.

A report from Dr. Kane on May 9, 1940, stated that the child had fever, a marked stomatitis and had developed a swelling in the left side of the abdomen. Urinalysis was negative. The mother stated that she thought the child had strabismus.

On June 5, 1940, the child entered the University Hospital at Ann Arbor, Michigan, and I am indebted to the Department of Pediatrics for the following notes:

The essential points in the examination at this time disclosed superficial venous engorgement of the head; ears painful to examination; edema of the eyelids; mild strabismus; bleeding from the mucous membrane of the mouth; enlarged, hard, movable cervical and maxillary nodes; heart and lungs negative; abdomen asymmetrical with bulging of the left flank extending to midline, to symphysis and up to costal margin; edema of the ankles.

The Kahn test was negative. Urinalysis revealed a trace of albumin, otherwise the urine was negative. Blood count disclosed the following: (June 6, 1940) red cells, 2,000,000; white cells, 8,000; hemoglobin, 40 per cent; polymorphonuclears, 54 per cent; eosinophiles, 15 per cent; lymphocytes, 26 per cent; monocytes, 6 per cent. On June 10, 1940, after transfusion, the hemoglobin was 72 per cent, and the white count 5,100. Blood non-protein nitrogen was 62 milligrams per 100 c.c. on June 7, 1940.

A tentative diagnosis of intracranial metastasis was made. There were no definite localizing symptoms.

The child died on June 12, 1940. Permission for autopsy was not granted.

Pathologic report gave the following data:

Gross description: The kidney weighed 72 grams. There were remnants of fetal lobulation. The color was pale grayish-brown. A few subcapsular, dilated, stellate veins were seen. In the cortex very few of the normal markings were seen. The cortex was bloodless and clay-colored. The width of the cortex was 4 to 5 mm. Pelvis and major calyces were normal.

Microscopic description.—In several sections of the kidney, the outstanding change was the presence of large cellular infiltrations between the tubules of the cortex and the medulla, separating most of the tubules so that the interstitial spaces were two to three times wider than the tubules. The majority of the cells could not be identified.

Aside from some eosinophilic granulocytes, the majority of the cells had slightly rounded to oval nuclei in which there was considerable variation in the quantity of the chromatin. Cytoplasm was distinct only in a few of the cells and this cytoplasm stained poorly. There were occasional nuclei that were indistinct. The distribution of the cells resembled that observed in leukemic condition. There were a few mitotic figures. There were occasional small cells with deeply staining masses of chromatin and basophilic to eosinophilic cytoplasm slightly suggestive of erythroblastic cells. Celloidin preparations were made and these were stained with Fonte's modification of Bielschowsky's stain, Giemsa's stain and H. and E. Diagnosis: myelocytoma of the kidney. (Dr. Carl Apfelbach.)

The sections were sent to the Carcinoma Registry of the American Urological Association. The results of the study of the slides are given in the accompanying table.

Date	Diagnosis	Signature
12–10–40	Aleukemic myelocytoma with diffuse distribution	G. R. Callender
10– 3–41	Myelocytoma, aleukemic, diffuse	Alfred Golden
10– 6–41	Myelocytoma, aleukemic, diffuse	J. E. Ash
11–12–41	Leukemic (myeloid) infiltration, or Hodgkin's disease	F. Parker, Jr.
12– 4–41	Myeloid infiltration (aleukemic myelocytoma)	N. C. Foot
2– 1–42	No change	G. R. Callender

DISCUSSION

Due to the presence of a large swelling in the right kidney area, coupled with changes in the pyelogram, a tentative diagnosis of Wilms' tumor was made. The presence of slight changes in the left pyelogram resulted in a discussion of the possibility of a bilateral Wilms' tumor. However, the changes in the left pyelogram were not marked and it was difficult to reconcile them with a Wilms' tumor.

The very rapid response to the roentgen therapy at once raised my suspicions that perhaps this was not a Wilms' tumor. My suspicions were based on the fact that I had never before seen a Wilms' tumor decrease so rapidly and to such a marked degree following six days' treatment with roentgen-ray.

In casting about for other causes of renal enlargement the pos-

sibility of leukemia was discussed, and further careful studies of the blood were made; but the unanimous opinion was that the blood picture failed to verify a leukemia. Furthermore, there were no evidences of leukemia, such as enlargement of the spleen and enlargement of lymph nodes. Interesting, too, in this discussion regarding the possibility of leukemia is the fact that the blood studies at the University of Michigan Hospital were negative and that they were made shortly before the child died.

At operation the kidney was uniformly enlarged. The surface was smooth, not nodular, and there were no sharply defined tumors such as occur in Wilms' tumor. Having once seen a Wilms' tumor in which the shape of the enlarged kidney was normal, with a resulting normal pyelogram, and because the kidney responded so rapidly to roentgen therapy, and because there was nothing to arouse my suspicions that I was dealing with a leukemia, a nephrectomy was performed.

SUMMARY

Histologic studies of the last two decades have brought about a better interpretation of malignant tumors arising from mesenchymal tissues. In former years this sort of tumor would probably have been classified merely as a sarcoma. Localized proliferations of lymphatic or myelogenous tissue have been described with greater frequency in recent years so that we now recognize them in our clinical differentiations. It is significant that not all localized forms of lymphosarcoma and myelosarcoma are associated with a leukemic reaction in the peripheral blood, hence this characteristic cannot be relied upon in differential diagnosis. In contrast to other sarcomas, the response to radiation is usually marked in the lymphatic and myelogenous neoplasms.

METASTATIC VERTEBRAL OSTEOMYELITIS COMPLICATING PROSTATIC SURGERY

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The record of an acute osteomyelitis of the spine complicating prostatic surgery has not, up to this time, been found in the medical literature. It hardly seems possible that such a complication is actually new; it is more probable that it has been overlooked or misdiagnosed. The most common misdiagnosis has been a metastatic cancerous lesion originating in the prostatic gland. The three cases herewith presented illustrate a definite relationship between urinary tract infection and acute vertebral osteomyelitis. In the light of Batson's research, they offer evidence of a hitherto unsuspected etiology for acute bone infections in all cases of acute osteomyelitis of the spine not due to trauma. They are cases of acute pyogenic osteomyelitis similar to cases described by other writers who have been very close to this explanation but who have never been able to discern the true pathway of infection because of the widespread disease which tends to camouflage the disappearance of the disease trail in the tissues between the primary and secondary lesions.

Case 1.—H. G., aged sixty-six years, was admitted to the New Haven Hospital September 10, 1939, with complete retention of urine of six hours' duration. The history of prostatism dated back over a three-year period, with gradually increasing frequency and diminution in the size and force of the urinary stream. There had never been any burning or smarting on urination. The patient's family physician had made an unsuccessful attempt to catheterize him about six hours after complete retention, some bleeding had followed, and the patient was admitted to the Urological Service. The past history is unimportant except for typhus fever at the age of thirteen years, from which the patient recovered rapidly and without complications. The family history is one of unusual longevity.

On admission, the vital signs were normal, although the patient seemed to be in great distress until he was relieved by the passage of a No. 16 rubber catheter. The head and chest with organs were normal. The bladder contained 600 c.c. of uninfected urine with specific gravity of 1.007, a trace of albumin, no sugar, and a few red blood cells.

Rectal examination disclosed a very large, elastic prostatic gland. Physical examination was otherwise essentially normal. The extremities and reflexes were normal. The non-protein nitrogen was 32 milligrams per cent; Kahn, negative; red blood cells, 4,200,000; hemoglobin, 13.5 grams; white blood cells, 13,200; polymorphonuclears, 89; lymphocytes, 10; monocytes, 1; blood pressure, 168/85.

Although the vital signs were normal, the patient tolerated the ure-

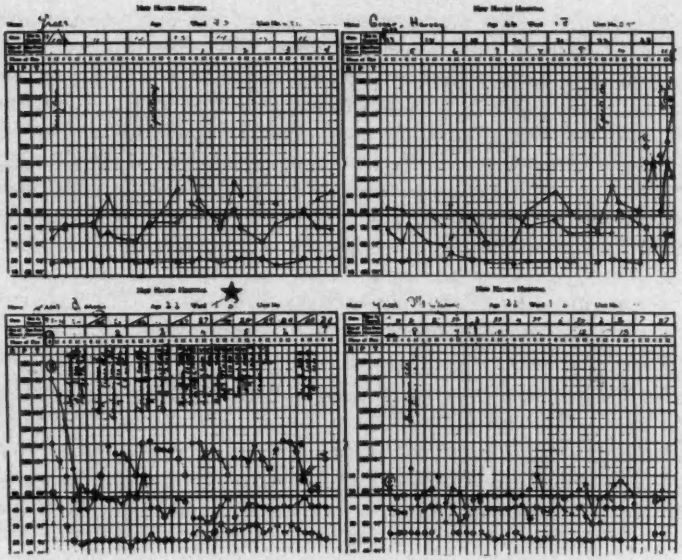

Fig. 1. Case 1. Photograph of hospital record of temperature, pulse, and respiration chart for the first four weeks.

thral catheter poorly. He had bladder spasms, and the bleeding was sufficient to cause obstruction of the catheter with clots. A suprapubic drainage was therefore done under local anesthesia two days following admission, and the patient was relieved immediately of bladder spasms. His temperature "spiked" to 101 degrees the following day and then remained normal for one week. The excretion of phenolsulphonephthalein was 50 per cent in two hours; and the non-protein nitrogen ranged from 32 to 34 milligrams per cent. Ten days after the primary suprapubic drainage, a second-stage prostatic enucleation and bilateral vasectomy were done under ethylene anesthesia. The prostatic tumor, which weighed 65 grams, was enclosed in a fibrous capsule and was readily enucleated. There was moderate bleeding from the prostatic

bed, which was controlled with a Pilcher bag, and the bladder was drained with a large, straight, rubber tube. The patient had been receiving 45 grams each of acid sodium phosphate and urotropin per day previous to his second-stage operation.

The day following his second operation, the patient developed a chill and a temperature of 105.4 degrees F.; and, on the next day, a temperature of 106 degrees, F. He was acutely ill, restless, confused,

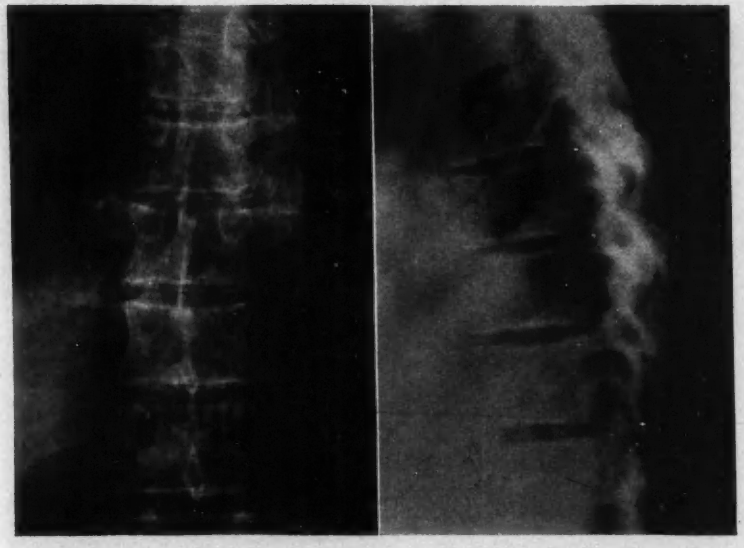

Fig. 2. Case 1. Normal-appearing roentgenograms four weeks after clinical localization of the disease process.

and irrational. Several blood cultures were taken. On the second postoperative day, one culture showed a non-hemolytic streptococcus and B. coli. Three days after the second operation, the white blood count rose to 30,000; and the non-protein nitrogen to 77 milligrams per cent. The blood carbon dioxide was 30 per cent; and the blood chloride, 102 milligrams per cent. The red blood count dropped to 2,800,000; and the hemoglobin to 58 per cent.

On the fourth postoperative day, the patient complained of pain in the left lower chest. The physical findings were inconclusive, and portable roentgenographic examination of the chest was indeterminate. On the fifth postoperative day he complained of pain in the right kidney region, where some tenderness was found, and a right pyelitis was suspected. This persisted for two days only. Within the next week,

the pain finally became localized in the mid-dorsal region, radiating laterally on each side. During the week of severe illness, swelling and redness of the right wrist and ankle appeared and persisted for five days.

The patient was treated with blood transfusions every other day for one week, supplemented with daily intravenous glucose and saline. He showed considerable abdominal distention and had moderate hiccough,

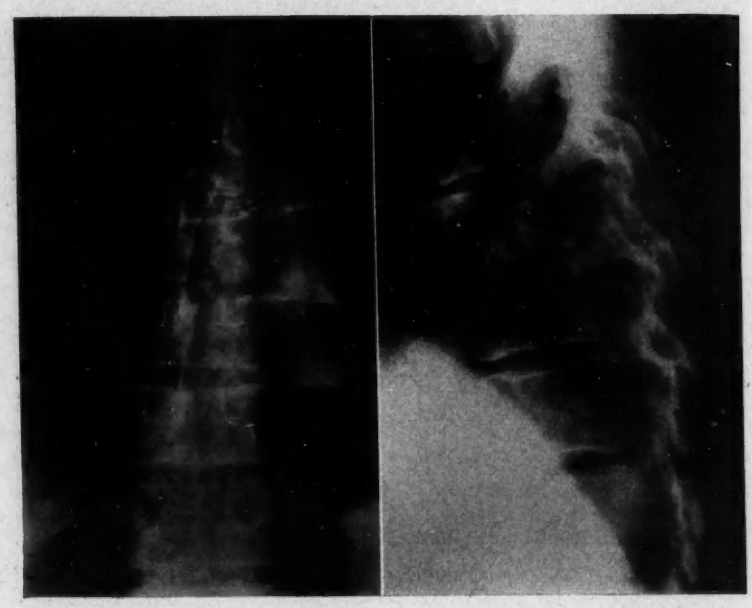

Fig. 3. Case 1. Roentgenograms, seven weeks after clinical localization of the disease, showing a destructive process of adjacent portions of the eighth and ninth dorsal centra, narrowing of the included intervertebral disc space, and an associated paravertebral soft tissue mass.

although he did not vomit. He was given prontylin, 45 grains a day, by mouth. On the tenth day after the second-stage operation, the temperature became normal and remained normal except for one or two elevations per week of from 99 to 100 degrees F. The suprapubic wound healed in twenty days, but full control of urination was not obtained until the end of the fourth week. The patient continued to complain bitterly of localized pain in the dorsal region, although nothing was visible or palpable except some tenderness over the eighth and ninth dorsal vertebræ. Roentgenograms of the dorsal spine October

31, five weeks following the second-stage operation, failed to show any bony change. Since the pathologist had reported that the prostatic tumor was a benign tumor infiltrated with cancer, a clinical diagnosis of metastatic cancer in the dorsal region was made.

Roentgenographic reëxamination of the spine two months following the second prostatic operation revealed narrowing of the intervertebral disc space between the eighth and ninth dorsal bodies with moderate

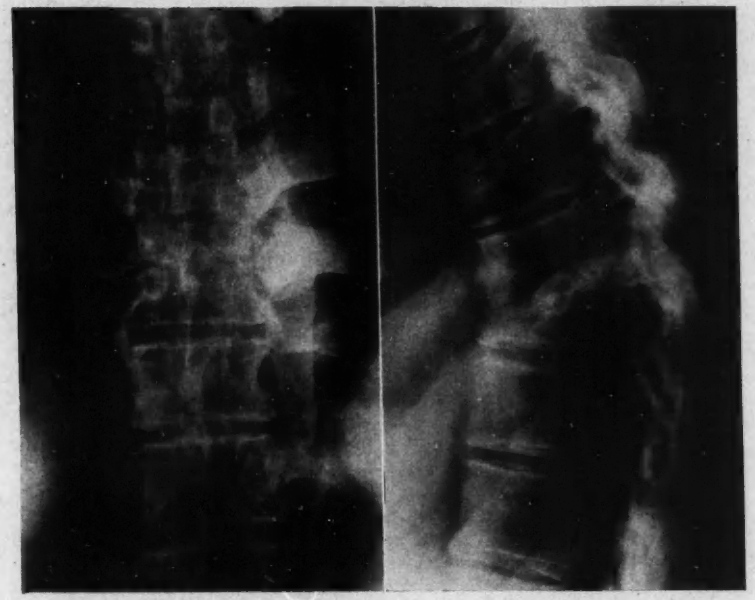

Fig. 4. Case 1. Roentgenograms, two and one-half years after discharge from hospital, showing late result with bony fusion of the wedged vertebræ and persistence of the paravertebral soft-tissue mass.

destruction of the vertebral centra on either side of the narrowed joint space. The destruction was more marked anteriorly. A paravertebral soft tissue mass was present on both sides opposite the seventh to the tenth dorsal bodies. The x-ray diagnosis was a destructive process involving the eighth and ninth dorsal vertebræ. The question of metastatic malignancy was again raised.

There gradually developed localized redness and slight swelling in the dorsal area. Because of the continued pain, which had been controlled with difficulty by sedatives, and the presumptive diagnosis of metastatic cancer, a course of fractionated irradiation for a total of

1,530 roentgens measured in air was given to the dorsal region. There was not any significant palliative response to radiation. The patient was discharged on December 5, 1939, approximately three months following his admission. The urine was clear and free from infection. He was seen as an ambulatory patient throughout the winter. A gibbus appeared in the dorsal area in the middle of December, and the pain continued, the patient requiring a daily sedative for nine months.

At the present time, the patient continues in good health. Rectal examination shows a prostatic gland which is not enlarged but which is somewhat firmer than normal and adherent to the adjacent structures. Conventional and laminagraphic reëxaminations May 15, 1942, two and one-half years following the patient's discharge from the hospital, reveal bony union of the eighth and ninth dorsal bodies with a moderate degree of bony lipping and minimal sclerosis at the site of fusion. There is evidence of anterior wedging of the involved bodies with a prominent kyphos in this region. Bony bridging is present between the ninth and tenth dorsal centra. The paravertebral soft tissue mass shows no significant change. A metastatic survey, done at this time, reveals no roentgen evidence of metastatic tumor.

Case 2.—L. M., aged sixty-five years, was admitted to the Urological Service June 19, 1941, complaining of frequency of urination. The urinary frequency was of only eight weeks' duration but had been rapidly progressive, and the patient was voiding every thirty minutes in the morning and about every hour at night, without pain, burning, or smarting. The size and force of the urinary stream had become diminished, although the patient had never had acute retention of urine and had never been catheterized. The family and past histories were irrelevant. Physical examination showed the patient to be a small man in good condition. A small right hydrocele was present. Rectal examination revealed a normal rectal sphincter and a prostatic gland which was three times normal size, elastic, and free from nodules and adhesions. Examination of the urine disclosed a trace of albumin and a trace of sugar but no infection. The bladder capacity was 400 c.c., and there was no residual urine. Cystoscopy showed moderate trabeculation of the bladder wall without diverticula or stones. There was a moderate-sized median lobe and lateral lobe enlargement of the prostate. The vital signs were normal. The extremities did not show any deformity, and the reflexes were undisturbed. The red blood count was 4,800,000; hemoglobin, 94 per cent; white blood count, 9,000; blood pressure, 128/72; phenolsulphonephthalein, 43 per cent in two hours; non-protein nitrogen, 30 milligrams per cent; and fasting blood sugar, 80 milligrams per cent. The patient never showed sugar reaction in the urine after admission.

On June 24, 1941, five days after the patient's admission, a transurethral resection was done. An attempt was made to use spinal anesthesia, but the return was slightly bloody; consequently, nitrous oxide

anesthesia was successfully substituted. Hemostasis was well maintained at operation, but that evening the patient complained of bladder distress. The catheter failed to drain well. The original catheter was removed, another was inserted, and 600 c.c. of blood-stained urine was obtained. Tension was applied to the new catheter for two hours only, after which there was never any bleeding or discomfort. Sulfathiazole, 2 grams per day, was given from the operative day on for one week.

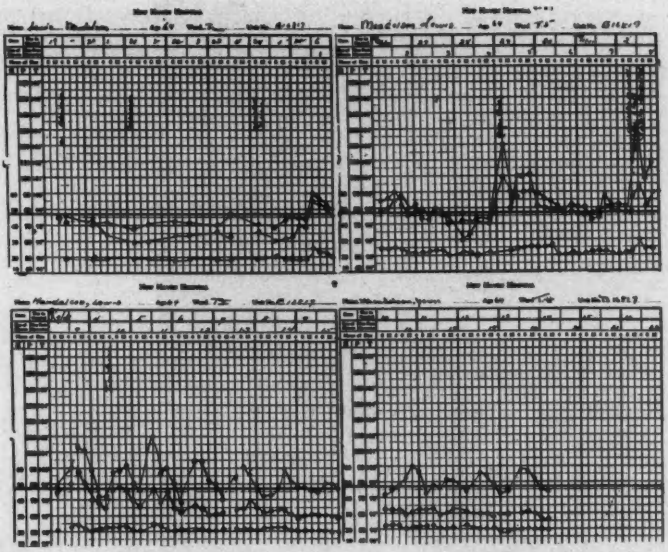

Fig. 5. Case 2. Photograph of hospital record of temperature, pulse, and respiration chart.

The patient's temperature rose to 100 degrees F. on the first and second days after operation and was then normal for two days. The urethral catheter was removed on the fourth postoperative day, and the patient was allowed out of bed. He seemed weak and looked ill. On the fifth day, he developed a chill and a temperature of 103 degrees F. He was voiding 100 c.c. of urine at each urination with ease, and the bladder was not palpable. The blood pressure reading was 80/40 and gradually reverted to a normal reading in the next four days. The patient's temperature varied from 98 to 100 degrees F. daily with the exception of the eighth postoperative day, when he had a second chill, and his temperature rose to 104.4 degrees F. The catheter was reinserted at this time, but less than 100 c.c. of urine was obtained from the bladder.

On the fifth postoperative day, when he had had the first chill, the patient had complained of severe backache. This pain continued and was so severe in the lumbar region that morphine was given. There was not any local redness or swelling over the spine, but the patient held his back rigid and refused to move because of the pain. He reluctantly got up each day and continued to appear ill. His blood count

Fig. 6. Case 2. Roentgenogram, three months following transurethral resection, showing narrowing of the intervertebral space between L 1 and L 2 with destruction of adjacent portions of the participating vertebral bodies.

on the day of the first chill was red blood cells, 2,800,000; hemoglobin, 52 per cent; white blood count, 43,000; with 76 per cent polymorphonuclears. He was given one blood transfusion of 500 c.c. On the eighteenth day postoperatively, the red blood count had returned to 3,000,000, and the white blood count had fallen to 9,000. Since there was nothing visible nor palpable in the lumbar region, it was thought that the back pain was due to the position which the patient took in bed.

He was discharged on the twentieth postoperative day, voiding 200 c.c. of clear urine at each urination. The prostatic tissue removed at operation had proved to be benign on histologic examination.

The patient was re-admitted to the New Haven Hospital on September 8, 1941, a little more than two months following operation, complaining of his backache but complaining more of severe constipa-

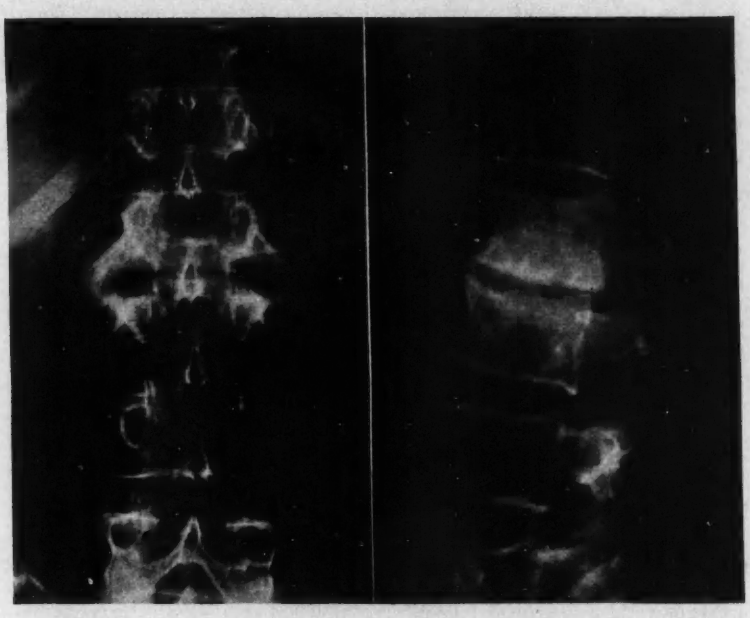

Fig. 7. Case 2. Roentgenograms, nine months after transurethral resection, showing reparative phase of osteomyelitic process with abundant periosteal new bone formation and bony bridging.

tion. Physical examination disclosed abdominal distention, but there was no redness or deformity of the back. Urinations were normal, and the urine was free from infection. Blood pressure was 110/40; and temperature, 99.2 degrees F. The patient was admitted at this time primarily for a gastro-intestinal series. Stool examination showed no occult blood. The gastro-intestinal x-ray series was reported indeterminate with the exception of hypomotility of the small intestine and colon. The blood count was 3,900,000 red blood cells and 13,500 white blood cells, with 87 per cent segmented polymorphonuclears.

The patient was given cathartics for the chronic constipation with good result. He returned again October 28, 1941, three months follow-

ing operation, still complaining of pain in the lumbar region. Aside from spasm of the erector spinæ muscles, nothing could be found on local examination. The urine remained normal. Conventional and laminagraphic examinations of the lumbar spine at this time revealed a symmetrical, scalloped destruction of the adjacent intervertebral portions of the first and second lumbar bodies with considerable narrowing of the intervertebral disc space. The destruction involved particularly the lateral aspects of the bodies anteriorly and posteriorly. There was moderate sclerosis of the involved centra with bony bridging between them on both sides. No soft tissue paravertebral mass was observed. An x-ray diagnosis of osteomyelitis was made. A review of the previous gastro-intestinal examination revealed moderate narrowing of the intervertebral disc space between the first and second lumbar bodies with loss of the outlines of the inferior cortical plate of the first lumbar centrum and anterior portion of the superior cortical plate of the second.

The patient was relieved with rest in bed and a brace to his back and is now entirely relieved of symptoms. Roentgenographic re-examination of the lumbar spine, March 4, 1942, revealed further narrowing of the intervertebral disc space between the first and second lumbar bodies and an increase in the amount of bony bridging. No progression in the bony destruction was demonstrated.

Case 3.—D. B., aged seventy-one years, was admitted to the Neurological Service on November 20, 1940, for treatment of metastatic carcinoma of the lumbar spine. He had had two previous admissions to a neighboring hospital, and the report of the previous hospital experiences was obtained from the records of that hospital.

The patient's first hospital admission was on December 8, 1937, with a benign overgrowth of the prostatic gland. He had had acute retention of urine for eight hours prior to admission and had a further history of some frequency of urination for one month. There had been no loss of weight. His past history disclosed the usual childhood diseases without complications; a nervous breakdown three years previously controlled with six months' rest; and an attack of influenza in 1892 without sequelæ. The family history was non-contributory. The physical examination showed him to be in good condition. The vital signs were normal. The blood pressure was 130/70; pulse, 76. The bladder had not previously been catheterized and contained 720 c.c. of uninfected urine. The prostate was about three times normal size, and the enlargement was characteristic of benign growth. The blood count was normal; the non-protein nitrogen, 26.5 milligrams per cent; and phenolsulphonephthalein excretion, 48 per cent in two hours.

On December 9, 1937, the day following the patient's admission, a suprapubic cystotomy was done under spinal anesthesia. The patient's temperature rose to 100 degrees F. the next day but subsided in two days. A second-stage suprapubic enucleation was done on December

16, 1937, under avertin anesthesia. The prostatic tumor, which weighed 25 grams, was easily enucleated. A prostatic bag and suprapubic drainage tube were used for two days. The patient's temperature, which was 99 degrees F., on the first postoperative day, gradually rose to 104 degrees F. on the eighth day. During the first week, he was out of bed, suffered from abdominal distention, became irritable, and had chilly sensations. He complained of low backache on the eighth day following

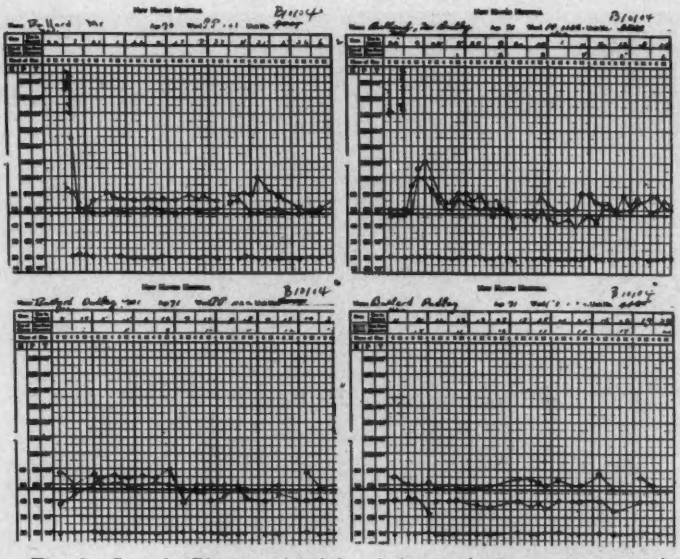

Fig. 8. Case 3. Photograph of hospital record of temperature, pulse and respiration, three and one-half years after onset of vertebral osteomyelitis. Slight elevation of temperature.

the second operation. Blood culture showed a hemolytic streptococcus. Glycosuria and hyperglycemia appeared for the first time. He was treated with sulfonamide and insulin.

During the second week, his temperature ranged near 102 degrees F. He developed aching knee joints without swelling. He complained bitterly day and night of low backache and pain in his legs. He refused to sit up because of the terrific backache. At the beginning of the third week, while up, he fainted and fell to the floor. His back was strapped with adhesive, and fluids were forced to 5,000 c.c. a day. At times he suffered hiccoughs. By January 3, 1938, eighteen days postoperatively, his temperature had returned to normal, and he began to sit up one-half hour per day. Roentgenograms of the lumbar region

were interpreted as showing hypertrophic arthritis of the fourth and fifth lumbar vertebræ. For the next two weeks he showed gradual improvement but was "drenched" with perspiration daily. The patient was discharged from his first hospital admission on January 19, 1938, forty-four days after the second operation.

He was re-admitted to the same hospital on August 29, 1939, complaining of light-headedness and weakness in the legs of one month's

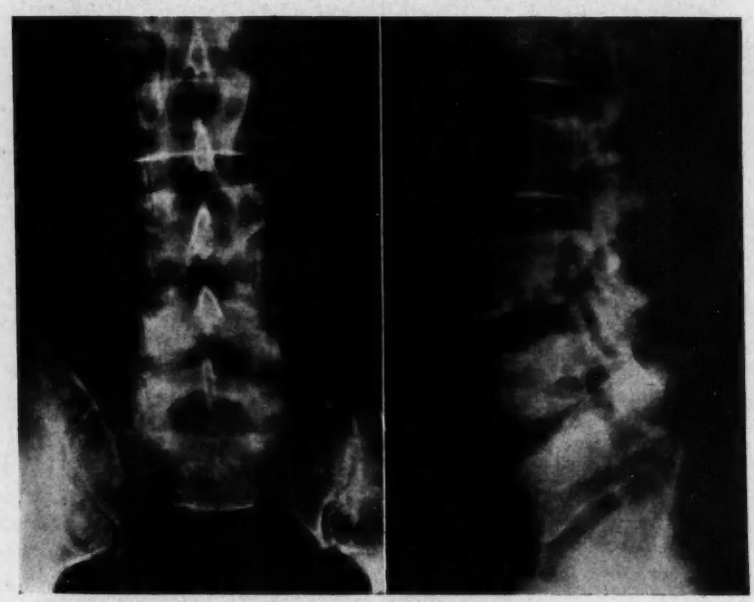

Fig. 9. Case 3. Roentgenograms, approximately three years following suprapubic prostatectomy, showing an extensive sclerosing and destructive process involving L 3, L 4 and L 5 with moderate narrowing of the included intervertebral disc spaces.

duration. These symptoms occurred sometimes simultaneously and at other times independently. Examination at this time showed the patient to be in fair condition. Blood pressure was 128/70; red blood count, 5,200,000; hemoglobin, 108 per cent; white blood count, 6,600; with 65 per cent polymorphonuclears; and non-protein nitrogen, 35.6 grams per cent. Examination of the reflexes showed that the knee jerks were sluggish; the abdominal and cremasteric, absent; Rhomboid, partially present on the right; and the Babinski, absent. A gastro-intestinal series done at this time suggested an enlargement of the head of the pancreas.

On November 20, 1940, nearly three years following his first hospitalization, the patient was admitted to Dr. W. J. German's Neurological Service at the New Haven Hospital. Early in September, 1940, the patient had tried to get up and had discovered that he could not stand alone. He had not been able to walk or to stand for the past three months. He still had severe pain in the lumbosacral region with bilateral sciatic radiation. The pain was worse when he was in the erect position. His legs had become very weak. Roentgenographic examination of the lumbar spine revealed slight scoliosis in the dorsolumbar region with convexity to the right. There was moderate narrowing of the third and fourth lumbar intervertebral disc spaces with irregular destruction of the adjacent cortical plates. The body and laminæ of the fourth lumbar vertebra and the portions of the third and fifth lumbar bodies adjacent to the narrowed disc spaces showed sclerosis. The pedicles of the fourth lumbar vertebra were obliterated. Bony bridging was present between the third and fourth lumbar centra. No paravertebral soft tissue mass was visualized. The x-ray diagnosis was involvement of the third, fourth, and fifth lumbar vertebræ by osteoplastic metastatic tumor, and the question of a primary carcinoma in the prostatic gland was raised.

A laminectomy was done by Dr. German on November 27, 1940, under avertin anesthesia. The third and fourth lumbar spinous processes were removed. The dura was not opened. There was thickening of the ligamentum flavum but no evidence of tumor. A small quantity of slightly cloudy fluid appeared at the paravertebral region beneath the muscles and just superficial to the lamina on the left side. Culture of this fluid grew a large gram positive bacillus and a Staphylococcus aureus. The patient was discharged on December 23, 1940. He ran a down-hill course and died in June, 1941, four and one-half years following surgical treatment of the benign prostatic obstruction. An autopsy disclosed chronic osteomyelitis of the lumbar region without evidence of primary or secondary cancer.

DISCUSSION

Incidence of Acute Pyogenic Spinal Osteomyelitis.—In a series of 1,500 cases of pyogenic osteomyelitis, Kulowski found that the spine was involved in 3.94 per cent. Acute pyogenic spinal osteomyelitis is infrequent in individuals of the prostatic age. The average age for osteomyelitis of the spine is thirty-one years (Kulowski). The male is affected twice as often as is the female. In 102 cases of spinal osteomyelitis, the location was cervical in eight cases, dorsal in thirty-one, lumbar in fifty-one, sacral in nine, and coccygeal in three. In another series of seventy-one cases reported by Wilensky, the location was cervical in twelve, dorsal

in nineteen, lumbar in thirty-one, and sacral in nine. Thus we see a predilection in the lumbar region for this lesion.

Symptoms.—The symptoms of acute osteomyelitis of the spine are clinically dramatic. They are characterized by rigors, high fever, prostration, delirium, abdominal distention, and diarrhea. A marked leukocytosis is usually present. The local pain and the neurologic manifestations frequently suggest the site of the lesion. Case 3 illustrates this last phenomenon. Blood cultures are frequently positive. Many case reports of acute osteomyelitis of the spine contain reference to the high percentage of urinary tract infections. Carson reports four cases of acute osteomyelitis of the spine in which, he states, there were two factors common to all: Staphylococcus aureus septicemia and urinary tract infection. The general symptoms may be acute or subacute, and some days may elapse before local signs appear. Movement usually causes pain. In Carson's four cases of acute spinal osteomyelitis, the localized pain noted as "backache" occurred in nine days, one month, three months, and nine months respectively from the onset of the primary infectious lesion. In the authors' three cases, pain in the back occurred on the fourth and fifth postoperative days respectively in the first two cases and on the eighth postoperative day in the third case. The pain was fairly well localized in the two patients who had lumbar lesions but was generalized in the patient with the dorsal lesion. In the latter case, the pain simulated successively that of an atelectasis of the lung and of a right pyelitis prior to its localization. In all three cases, the back pain was always excruciating and, in the third case, radiated laterally on both sides. The diagnosis in the first case was thought to be metastatic carcinoma, because the patient had a cancerous lesion of the prostate. In the second case, the organic lesion was not seriously considered. In the third case, the correct diagnosis was made only after laminectomy performed three years from the probable beginning of the osteomyelitic lesion. In Carson's series, changes in the bones demonstrable by x-ray occurred anywhere from two to fourteen months; in the authors' three cases, in two months, three months, and two years respectively from the time of the operative procedures.

It is difficult to make clinically the diagnosis of an early lesion of osteomyelitis of the spine, since it may imitate many other

lesions. Kulowski states that the following clinical diagnoses were made in cases of pyogenic spinal osteomyelitis subsequently proven by autopsy: tuberculosis of the spine, appendicitis, perinephritic abscess, arthritis of the spine, pneumonia and empyema, mediastinal malignancy, soft tissue abscess, meningitis, lumbosacral strain, sciatica, mycotic lesion, and ureteral obstruction. The mortality in cases of acute spinal osteomyelitis varies from 25 to 71 per cent.

Roentgenologic Considerations.—Narrowing of the intervertebral disc space, irregular destruction of adjacent portions of the vertebral bodies, varying degrees of sclerosis of the participating vertebræ, and rapid proliferative periosteal new bone formation constitute the essential diagnostic features of the cases presented. The presence of an associated soft tissue paravertebral shadow tends to confirm the diagnosis. These findings coincide with the accepted roentgenologic appearance of pyogenic osteomyelitis of the spine. At an earlier stage focal areas of destruction may occur close to the disc. One is then dependent on the rapid spatial alteration in the intervertebral disc for recognition of the process. When the disease occurs primarily in the posterior vertebral processes, painstaking roentgenographic exploration may be necessary, and the diagnostic difficulties are enhanced. Later in the disease invasion of the entire spongiosa may occur with subsequent collapse of one or more vertebræ and bony fusion. The degree of involvement is probably dependent on the type of organism, the stage of the disease, and the treatment. Satisfactory data are unavailable for estimating the lapse of time necessary for the development of the earliest roentgenographic findings. In the first case presented, bony changes were lacking, on satisfactory roentgenograms, four weeks after definite clinical localization of the disease. It is possible that sectional roentgenography, by eliminating the overlying confusing shadows, may contribute to the earlier recognition of the initial focus. The value of repeated examinations in the presence of well-defined, persistent symptoms cannot be overemphasized.

In the face of a known primary carcinoma in the prostatic gland, the diagnostic difficulties are augmented. The changes in the bone with osteoplastic metastases may simulate those seen in pyogenic osteomyelitis of the spine. Here, rigid adherence to the known differential behavior of the intervertebral disc in infection

and malignancy should minimize the possibility of error. The disc is rarely involved directly by metastatic tumor. The narrowing of the intervertebral space occasionally encountered in metastatic malignancy occurs as a late sequel, the result of extension of the intervertebral disc into the involved vertebral body. Usually, at this time, multiple involvement at different levels is to be found. It is not uncommon to find extensive replacement of the entire spine by osteoplastic metastases without evidence of collapse of the vertebræ or narrowing of the intervertebral spaces. Finally, on the basis of chance, the two processes may coexist. A correct roentgenologic interpretation often cannot be made without adequate consideration of the etiologic, pathologic, and clinical factors, together with the roentgenographic findings.

Etiology.—The portal of entry for acute pyogenic osteomyelitis of the vertebræ has been recognized as (1) direct and (2) hematogenous. Kulowski has reported that of 1,500 cases of acute pyogenic osteomyelitis in general, only 3.94 per cent developed spinal lesions, so that infection does not spread through the blood stream from one bony lesion to another very often. Blood stream infections are common, but acute vertebral osteomyelitis is rare. The so-called typhoid spine and gonococcal arthritis of the spine have been explained on a blood-borne basis. Many typhoid patients have urinary tract infections. Carson's four patients with acute pyogenic vertebral osteomyelitis all had urinary tract infections; two of them had had acute prostatitis preceding the back lesion, and two had had renal infections. Many patients suffering from pyogenic spinal osteomyelitis have urinary tract infections which are given little recognition in the consideration of the case as a whole.

All three of the prostatic cases presented developed an acute spinal osteomyelitis following operation. Two of the patients had the classical two-stage suprapubic operation; and the third, a transurethral resection. There was nothing in the histories to indicate that such a complication should be expected. All three patients showed certain postoperative symptoms in common. The immediate convalescence was unusually stormy and severe. They all had chills and "spiking" temperatures, in spite of urinary antiseptics and large fluid intake. All three patients suffered from

weakness or prostration, perspiration, abdominal distention, hiccoughs, restlessness, and irritability.

Since these three patients did not present any unusual problem at the beginning, did not have urinary tract infections, did not present any operative difficulty, did not lose any particular amount of blood at operation, and did not present any postoperative drainage problem, it must be admitted that their subsequent complication was in some way related to the operative procedure. All prostatic cases develop postoperatively a mild infection in the prostatic bed, whether suprapubic "prostatectomy," transurethral resection, or a perineal operation be done. In some patients infection is more severe than in others, despite all efforts to control it. All three of these patients received urinary antiseptics, although obviously they were ineffectual. It is fair to hypothesize that the infection of the spine in the three cases reported originated from the prostatic area or the operative field.

Batson has demonstrated a direct venous pathway from the prostatic and periprostatic veins to the vertebral veins by injecting the dorsal vein of the penis in cadavera and the same vein in the monkey. By the same method, he has been able to inject the cranial venous sinuses in seven out of ten cadavera, thus indicating the plexiform connections of the vertebral vein system along the lumbar, dorsal, and cervical segments. According to Batson, the vertebral veins are valveless, longitudinal, plexiform channels, which are under a lower hydrostatic pressure level than the pressure in the vena cava. Experimenting with the monkey, he found that, when the intra-abdominal pressure is increased, the venous flow to the vena cava is lessened, and the venous flow to the vertebral vein system is increased. Thus, the vertebral vein system is complementary to the portal and caval systems. Patients with postoperative abdominal distention and bladder infections present favorable conditions for the development of metastatic spinal osteomyelitis.

The three cases of acute vertebral osteomyelitis reported in this paper are clearly related to the infection of the prostatic urethra and the bladder following well-regulated operative procedures. In the light of Baston's work on the vertebral vein system, it seems logical that, since these veins drain the urethra and prostatic area, the true portal of entry of the infecting organism is through this

venous system. The authors believe that this may also be the portal of entry for vertebral lesions which occasionally complicate many of the infectious lesions, notably typhoid, gonoccoccal lesions, and undulant fever. All patients with spinal osteomyelitis should have a more thorough urinary tract study for infection, because this portal is the most logical of all indirect ways of transmitting an infection which involves the bodies of the vertebræ.

Treatment.—The early treatment of the severe backache in the authors' three cases could have been improved if the correct diagnosis had become apparent. However, conservative therapy was naturally applied. X-ray therapy, in the first case, as might be expected did not give a satisfactory result. In the second case, rest and a back brace were prescribed by an orthopedic surgeon with satisfactory result, after the exact diagnosis had been made. Surgical exploration clarified the diagnosis in the third case, but the disease was too far advanced to expect recovery. It is quite possible that the prolonged convalescence or even death of patients with similar lesions and with less dramatic symptoms has remained unsolved. In the future, prostatic cases complaining of severe backache complicating their postoperative course should be suspected of having an early vertebral osteomyelitis, and therapy should be instituted to prevent extension of the pathologic process, to shorten the convalescent period, and to diminish the mortality. All urinary tract infections represent a potential factor for the development of metastatic vertebral osteomyelitis.

SUMMARY

1. Three cases of acute metastatic vertebral osteomyelitis complicating prostatic surgery are given in detail.

2. The acute spinal lesion is undoubtedly related to the operative procedure.

3. The portal of entry is most probably the prostatic urethral veins which connect with the vertebral vein system.

4. It is suggested that urinary tract infection may be an etiologic factor in the development of acute pyogenic osteomyelitis of the spine.

Special Note: The authors wish to express their appreciation to Drs. Halford B. Kneale, Andreas E. Laszlo, and William J. German for the inclusion of Case III.

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FACTORS INFLUENCING MORTALITY AND MORBIDITY IN THE INTRAPELVIC RUPTURES OF URETHRA AND BLADDER

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Doctor Higgins suggested that I discuss with you briefly our experience with the traumatic injuries of urethra and bladder that occur as complications of fracture of the bony pelvis and to examine particularly the factors influencing mortality and morbidity in this group.

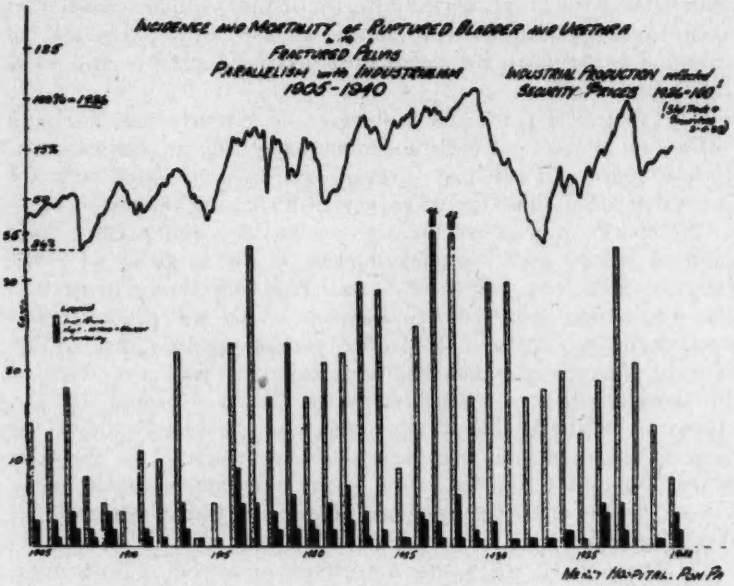
The subject, I think you will agree, is a timely one, for with the nation at war and mills and mines operating at peak capacity, the incidence will rise and surgeons will be confronted with the management of this type of injury in increasing numbers.

Traumatic injuries of the urinary bladder and urethra have been of special and particular interest to the surgeons of Pittsburgh over a long period of years. It is interesting to note in this connection that the first case in which the abdomen was opened for rupture of the bladder, indeed the first case of deliberate laparotomy which has been recorded, was performed in Pittsburgh within a stone's throw of Mercy Hospital, by Dr. Albert G. Walters. Dr. Walters received his doctor's degree at Koenigsburg and later became a pupil and assistant of the celebrated Diffenbach, supplementing his training later with Sir Astley Cooper in London. He practiced surgery in Pittsburgh until his death in 1876.

On January 12, 1859, he was called to attend a blacksmith, twenty-two years of age, who had been kicked in the abdomen and sustained an intraperitoneal rupture of the bladder. He made the correct diagnosis, could get no support from his consultants, but with the courage peculiar to the man, opened the peritoneal cavity widely, sponged away the effused urine, drained the bladder, and the patient recovered. The carefully documented report of this case was published in the *Medical and Surgical Reports of Philadelphia,* November 16, 1861, and created world-wide comment.

Forty-five years ago, the late R. W. Stewart of Mercy Hospital

staff, appalled by the terrible mortality and later morbidity occurring in fracture of the pelvis and rupture of the urethra and bladder, outlined a plan for the management of these patients that with few modifications is carried out at Mercy Hospital today. He designed special instruments for retrograde catheterization and published his technique in a monograph on injuries of the male urethra in 1896. Dr. George Davis of Chicago has recently modi-



fied and improved on Dr. Stewart's instrument with his interlocking sounds.

INCIDENCE

The incidence of urethral injuries due to external violence is not high. Herman sees an average of two cases per year. DeCourcey Wheeler reports an average of four cases per year at the London Hospital. Gilmour reports nine bladder and two urethral ruptures in eighty-one cases; Ashurst four urethral ruptures as complications in fifty-seven pelvic fractures; Culp and

Findlay two in thirty-five cases; Nolan and Findlay nine in 125 cases.

The incidence of traumatic ruptures of the urethra and bladder that occur as complications of fracture of the bony pelves is somewhat higher in the Pittsburgh district than in any other area recorded in the literature. This by reason of the large numbers of men employed in the heavy industries, especially the coal mines and steel mills. The incidence rises and falls with industrial activity. William O'Neill Sherman, in a personal communication, states that he has seen on an average of ten cases per year over a period of twenty-five years. His traumatic service is a larger one than ours at Mercy Hospital.

In an accompanying graph we are attempting to show the incidence and mortality of ruptured bladder and urethra with fracture of the pelvis and its parallelism with industrialism from 1905 to 1940. As an evidence of the rising incidence due to increased industrial activity in this district, fifty-two cases of pelvic fracture were admitted from January, 1940, to May of this year. Five cases of rupture of urethra and bladder complicating pelvic fracture have been admitted to the writer's service since Pearl Harbor. They were all, with one exception (an automobile accident), due to industrial accidents.

These injuries sustained in the coal mines are usually the result of the patient's being crushed between the mine timbers and a coal car, or by a fall of slate burying the patient beneath its weight. They are violent and mutilating in character; usually multiple fractures of the pelvis, intrapelvic rupture of urethra and bladder, frequently associated visceral injuries and shock so profound that many of them die (23 per cent on our service), either before or in spite of all remedial measures.

The mechanism of these injuries, the difference in the local and constitutional manifestations of those occurring anterior to the triangular ligament (straddle injuries) need not be discussed. The anatomy of the pelvic diaphragm, the location of the fascial planes that limit hemorrhage and extravasation, is well known, but, as Wheeler states, "that although the attachments of Colles' fascia are anatomically attractive, anatomical barriers are apt to be swept away by the oncoming tide of blood and urine helped in its depredations by subsequent infection."

DIAGNOSIS

Diagnosis is not difficult. With rare exceptions these patients are usually admitted in profound shock; there is extreme pain on movement; inability to move the legs which are generally rotated outward. The patient is unable to void and blood may be seen trickling from the meatus. Palpation of the iliac crests and compression of the pelvis causes great pain and crepitus can usually be elicited. The urethra is generally severed and displaced posteriorly and on rectal examination the rectum is compressed and a tender boggy mass may be felt and bony deformity outlined. Perineal and scrotal ecchymosis or hematoma may be present. Unless there is an associated rupture of the bladder, these patients do not extravasate early due to the reflex action of the sphincter. (In Young's case there had been no extravasation twelve hours after injury.)

If there is an associated rupture of the bladder, there is marked tenderness in the lower abdomen usually over the site of the rupture, and the rapidly developing hematoma produces a palpable tender mass, enlarging and distorting the lower abdomen. There is nearly always a traumatic ileus which makes the diagnosis of intraperitoneal rupture of the bladder or visceral injury difficult. As a rule however, the intraperitoneal injuries are more dramatic; greater shock, rigid board-like abdomen, absent peristalsis and great tenderness which in the extraperitoneal is more marked in the lower abdomen. In our opinion, the passing of a catheter in these patients is rarely indicated, and the information gained very misleading and unreliable.

In our opinion refinements of diagnosis in the intrapelvic rupture of urethra and bladder are rarely necessary. They have little or no influence on the management and may increase the gravity of the condition by unnecessary movement and manipulation of a badly fractured pelvic girdle. The delay necessary and additional trauma may be a factor in a mortality. We feel instrumentation of any sort is definitely contra-indicated in these cases.

MORTALITY

We have had an opportunity over a long period of years to examine causes of mortality and morbidity in this group.

The major cause of death in the intrapelvic group of patients that survive the primary injury is *urinary extravasation and sepsis.* In those with intraperitoneal complication, *i.e.* intraperitoneal rupture of bladder and associated visceral damage, the cause is extravasation and peritonitis.

The treatment must be rationalized to prevent these dangerous complications.

CAUSES OF MORBIDITY

1. Failure of early preservation of the continuity of the urethra, causing long standing complications difficult to correct.

2. Stone formation with grave damage to tract, unless prevented.

3. Loss of sexual power due to injury of the nerve supply or cavernous bodies.

4. Early infection of the soft parts of the pelvic cage with secondary involvement of the bony structures.

We submit the plan that we have evolved at Mercy Hospital for the management of these cases which has resulted in material reduction in the mortality and morbidity of these grave injuries and, to illustrate, recite in detail the history and management of one of the last five cases admitted to service of the writer this year in which there has been no mortality or morbidity. In three of the cases there was intrapelvic rupture of the urethra, one a complete rupture of the urethra anterior to the bulb from a combined crushing and straddle injury; one a ruptured bladder complicating a pelvic fracture as the result of an automobile accident.

Case 1.—N. M., aged twenty-three, coal miner, at 9:30 a.m., was crushed between two loaded coal cars and pinned there for some time. It was necessary to dig the coal away before he could be extricated. He complained of extreme pain in the lower abdomen and was unable to stand although he could move his leg, the movement causing extreme pain. He was rendered first aid at the mines and reached the hospital at 1 p.m. in extreme shock. Blood was oozing from the meatus. The patient had extreme pain and crepitus on manipulation of the iliac crests, legs rotated outward, and there was marked tenderness over a distended bladder. There was no rigidity in the upper abdomen, no nausea or vomiting. Upon rectal examination a soft boggy mass could be palpated. The blood pressure was 80/64. The usual measures were immediately instituted to combat the shock. One and one-half hours

later there was material improvement, the pressure rising to 118/80 and after a portable radiograph was taken, the patient was removed to the operating room.

Examination of the pelvis showed a longitudinal fracture involving the left side of the sacrum and extending upward in the midline. The fracture was a comminuted one with large fragment broken off the left side beginning about the midportion and extending downward to the level of the distal sacral segment. There was fracture of the inferior and superior rami of the left ischium involving the right pubic bone and also the junction of the descending ramus of the pubic bone and inferior ramus of the right ischium. There was little separation on the right, more marked on the left with fragments of the inferior ramus rotated downward. A chip fracture was found along the wide margin of the left ischium.

Operation was done under sodium pentothal anesthesia. With the patient in combined abdominolithotomy position, the abdomen was opened. There was massive hemorrhage in the space of Retzius, severe mutilation of the soft parts, the bladder distended, the urethra completely divided, the proximal and distal ends separated by at least an inch or an inch and a half. No loose spicules of bone were present. The space was evacuated, hemorrhage controlled. The bladder was opened and drained. A rapid perineal section was made, devitalized tissues debrided and a tube brought in a retrograde fashion through the bladder to the perineum and out through the urethra providing a splint from urinary meatus to abdominal wall approximating the torn ends of the urethra. No attempt at suture or anastomosis was made. The bladder was closed around a large Freyer tube. Sixty grains of sulfathiazole were placed in the prevesical space, and oozing was further controlled with packing. Two large drainage tubes were placed on both sides of the bladder. Before operation the patient received 500 c.c. of blood plasma and during operation 250 c.c. of 25 per cent glucose. Patient was returned to bed especially designed for this type of patient. The pelvis immobilized in a firm binder is suspended in a sling in a Bradford frame with pulleys attached so that patient can elevate himself for use of bed pan, et cetera. The legs are put in extension for correction of distortion and maintenance of approximation of the torn ends of the urethra.

He was given 30 grains of sulfathiazole daily and 1500-3000 c.c. intravenous glucose daily for the first five days. He was given a high acid ash diet and daily lavage of bladder with G. solution (Massachusetts General Hospital Formulæ).

Packing was removed on the fifth day; tubes were removed on the tenth day. The suprapubic tube was removed on the twenty-first day, and the tube that was used for splinting the urethra perforated and drained into the bladder for urethral discharge. The suprapubic wound healed kindly and the urethral catheter was removed the fifth week

after the injury. The patient voided freely through the urethra; there was no evidence of stricture.

In spite of extreme care the convalescence was complicated by a decubitus ulcer.

He was discharged two months and four days after admission, with urine normal. There was no disturbance of the urinary tract; there was slight disturbance of gait.

COMMENT

This case is presented because it is typical of the intrapelvic ruptures of the urethra that occur as a complication of fractures of the bony pelvis as a result of injury in the coal mines.

The mortality rises in this group who survive the primary shock—

1. When there is a long interval between the injury and operative care. This is minimized today by the organization and instruction of first aid crews at the mills and mines, so that the patient receives intelligent first aid care, is properly splinted and transferred to the hospital in the shortest possible time.

2. When the interval is protracted by unnecessary investigative procedures once the patient has reached the hospital.

3. When inadequate measures to prevent infection in terms of deviation of the urinary stream, hemostasis and drainage of the spaces, this procedure as indicated in the case report. In the long delayed case where extravasation has taken place, we supplement by dependent through-and-through drainage from the prevesical spaces through the perineum with tubes on both sides of the urethra.

At Mercy Hospital all patients with rupture except the milder forms that occur in the penile urethra, are subjected to diversion by cystostomy. We think it essential. We have seen secondary infection, sepsis and death occur in patients whose treatment has consisted of perineal sections, anastomosis and suture of the torn ends of the urethra, or by the simple passage of a catheter into the bladder in patients with partial ruptures, there is, almost invariably, leakage into the badly mutilated and devitalized tissues at the site of the rupture, with subsequent grave infection.

MORBIDITY

Stewart laid particular stress on the importance of immediate preservation of the continuity of the urethra. Failure to do so

resulted in serious complications. There is a large gap between the torn ends of the urethra. This space is filled with fibrous tissue, making extensive secondary operations for the correction of the defect necessary—procedures that are difficult and not always satisfactory in accomplishment. These complications have been noted and commented on by surgeons who have had to deal with this problem. Harrison recites the gravity of these complications in his excellent review of the cases seen at the Peter Brent Brigham Hospital. Young reports the gravity of failure of diversion of the stream and early preservation of continuity of the urethra.

We have not resorted to sutures and anastomosis in these cases; it is not necessary and lengthens the operation. The retrograde splinting of the entire urethra, with the legs in extension, has been sufficient for approximation and epithelization.

Stone Formation.—This is not uncommon in this group by reason of the marked increase in the excretion of the urinary calcium, stasis and infection, prolonged bed rest. In a previous paper we reported six cases of nephrolithiasis that occurred as a complication in this group.

Measures to prevent this complication are maintenance of the pH on the acid side, high acid ash diet, acidifying medication, frequent elevation of renal level, and large quantities of fluids.

Stricture Formation.—In our clinic the complication has been seen in greater frequency in the straddle injuries than in the intrapelvic ruptures.

Periodic dilatation is necessary.

Impotence.—This occurs as a complication in a small number of these cases, due to injury to the nerve and blood supply or to the cavernous bodies. Unfortunately, there is nothing one can do to prevent this distressing complication.

Impairment of Function of Weight-bearing and Movement.—We have been impressed with the amazing restoration of function as to weight-bearing and movement, walking, et cetera, in this group of patients with extensive damage in terms of multiple fracture of the bony pelvis. This is almost invariably true when the upper end of the femurs and acetabular areas are intact. We have seen these patients recover to such an extent that they were

able to carry on their former occupation as coal miners. The bad results are seen in the cases with serious infection of the soft parts of the pelvis with secondary involvement of the bony structures. The prompt attention to the urethral and bladder injuries and prevention of infection minimizes or eliminates these troublesome complications. Other factors in the restoration of function in these cases are meticulous postoperative care, the Russell type of extension with the legs in slight abduction, careful adjustment of the pelvic sling to prevent compression of the pelvis, early physiotherapy to improve the muscle tone.

COMMENT

We have shown by graph the incidence and mortality of ruptured urethra and bladder with fractured pelvis and the parallelism with industrialism among patients admitted to the surgical division at Mercy Hospital, Pittsburgh, Pennsylvania, from 1905 to 1940.

The gravity of these injuries is described and our observations on the factors influencing mortality and morbidity detailed.

The management of this type of injury is illustrated by the presentation of a typical case, from the time of injury to discharge and is submitted as a useful procedure in the care of these grave injuries.

Literature is reviewed and bibliography added.

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EXTRAVASATION OF URINE FOLLOWING USE OF KEARNS' BAG

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While the value of hydrostatic dilatation of the bladder in several types of bladder contracture is an accepted and generally employed therapeutic measure, there is but little written on the subject and, so far as I know, no published case reports of rupture of the bladder with extravasation of urine resulting from this procedure. Kearns, in 1932, and again with refinements in 1938, presented his ingenious rubber balloon apparatus.

As he states, "The advantages of the method are: (1) certain sustained and uniform dilatation of the bladder far beyond that previously attainable, (2) prevention of ureteral regurgitation, (3) decreased likelihood of hemorrhage, (4) avoidance of the danger of bladder rupture."

In a recent communication Dr. Kearns cites a case coming to his knowledge wherein a long sustained dilatation of an actively tuberculous bladder resulted in gangrene; also, within two months, the occurrence of his own first accident with a rupture of the bladder coincident with and at the point of contact with the rupture of the balloon. The bag was distended with 280 c.c. of water. The nature of the injury was immediately recognized and cystostomy performed. Recovery was prompt.

He therefore warns against the use of the bag in the presence of active infection, against other than brief gradual dilatation and gradual deflation, and against the use of any but fresh tested balloons. Should rupture of the bladder occur, it must be promptly recognized and cystostomy performed.

The method I have employed has consisted of first determining bladder capacity at cystoscopy and using the resultant amount as a base line to begin therapeutic dilatation. Treatments are spaced from one week to several months; the latter interval for maintenance.

Only a small increase, and frequently none at all, is attempted at each seance until symptoms are allayed. The amount of increase is determined chiefly by the patient's tolerance. A 10 c.c. Luer

valve-action syringe is connected with the balloon and a finely graduated beaker. The piston is advanced very slowly after a determined capacity is reached or the patient displays distress. The manometer has not seemed essential in treatment.

CASE REPORT

The patient was an obese woman, sixty-seven years of age, married and a housewife. The urologic diagnosis was (1) bifurcation of right ureter with single ostium at internal sphincter level with double ureters above the pelvic brim and double pelves and chronic pyelonephritis, right; (2) chronic interstitial cystitis.

From February, 1938, the bladder capacity was determined and charted seventeen times. It varied from 170 to 400 c.c. On November 11, 1941, the urine was free of pus and bacteria and on account of frequency and pain due to the chronic interstitial cystitis, the first therapeutic bladder dilatation with the Kearns' balloon was employed; 300 c.c. were accepted.

On December 10, dilatation was 400 c.c.; January 12, 1942, only 250 c.c., and February 11, 325 c.c. On March 11, she reported great relief from frequency and pain. On this date the dilatation was 350 c.c. You will note this was only 25 c.c. more than at the last treatment. The patient left the office without undue or unusual discomfort. She returned to the home of a relative a considerable distance from the city.

The following day there was hematuria, dysuria and gastric upset. A young physician in the neighborhood saw her. Two days later, March 15, her condition was for the first time reported to me by phone and I ordered immediate hospitalization. When seen she was in shock, had marked ileus and dehydration. On March 16 her response to intravenous fluids and supportive treatment was sufficient to justify exploration. Immediately beneath the rectus fascia, a large accumulation of dark red fluid was released. The exploring finger found a complete disassociation of the bladder from the pelvic wall on the left side. The finger entered a large necrotic defect in the left bladder wall. Drainage was established. Death occurred the following morning.

Autopsy revealed extravasation of urine, and purulent material, extending retroperitoneally from the left bladder wall along the course of the left ureter and surrounding the left kidney. Evidently a minute rupture occurred permitting gradual extravasation of urine and bladder wall necrosis.

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DISCUSSION

Dr. David M. Davis (Philadelphia, Pa.): I would like to mention another case of vertebral osteomyelitis which is similar to those described by Dr. Deming in all respects, except the manner of its onset. In this case, the patient had an ordinary benign prostatic hypertrophy. He entered the hospital where he underwent perineal prostatectomy. The convalescence from this operation was entirely usual, practically afebrile. The patient's incision healed in the usual length of time and he left the hospital practically free of symptoms, voiding normally and in excellent amounts. He returned to the outpatient department on two or three occasions. Six weeks after the operation at a time when he stated that he was perfectly well, I passed a No. 20 sound through his urethra, purely as a matter of routine to make sure that it was of the correct size. This sound entered the bladder very easily. I thought nothing of it. However, shortly after returning home, the patient had a very severe chill, his fever rose to about 105. He became distended, semi-delirious and had to be brought back to the hospital where he remained very ill for a long time, and finally developed this same excruciating pain in the middle of the back. After the lapse of some weeks, I don't remember the exact period, the persistence of this symptom caused us to investigate the vertebral column, and we found there an x-ray picture exactly like these which Dr. Deming showed. The pain was really excruciating, the slightest movement caused unusual pain, even lifting the corner of the bed clothes would make him cry out. However, after a while, the temperature fell and at that time the orthopedic surgeons recommended a bone graft, which the patient refused. He was finally able to leave the hospital, wearing a sort of brace or binder, and eventually made a complete clinical recovery as far as pain and disability were concerned.

Now, the urine during the stage of his actual illness contained nothing but staphylococcus in this particular instance. The urine, while reasonably clear after prostatectomy, was undoubtedly still infected at the time the sound was passed and the avenue of infection here must have been the same as when the infection follows immediately on the operative procedure.

If I have another moment, I would like to make a few random

observations, as Dr. Rathbun would say, about the question of the microscopic pathology of kidney tumors. While Dr. Cahill was showing the slides of the kidney tumor in his extremely interesting case, I couldn't help being impressed with the fact that I personally in my own mind, however far removed that may be from the facts, could not see any particular difference between this tumor and almost any hypernephroma. I have been led to believe that there is, unfortunately, some lack of objectivity in the usual examinations that are made of renal tumor. A great many pathologists possess fixed ideas, as it were, about the nature and origin of renal tumors and their descriptions of renal tumors which come to them are very prone to fit in with their own ideas. The only comment that can be made is that there are so many different ideas that they cannot possibly all be correct.

I try to be objective in my own work with tumors. It has seemed to me the most important thing you can do is to make many sections from many parts of every tumor to be examined. The best guide in getting the blocks for test sections is to look at the cut surfaces of the tumor. The cut surface of a typical hypernephroma always shows a variegated appearance. The color varies, the opacity varies, and so forth, and one should try to take a piece from every different appearing area in the tumor.

Certainly the presence of blood-filled spaces is an extremely common thing in hypernephroid tumors. In fact, it almost seems to me that if you hunt far and long enough, you will find them in practically every one.

In the early days of the study of renal tumors, some pathologist, whose name I cannot at this moment recall, felt thoroughly convinced that hypernephromas were essentially angiomatous in nature and so described them and theorized upon their method of origin.

We are still very ignorant of the natural history of renal tumors. It is possible that there is something to this idea of the relationship between hypernephroma and angioma, and it is possible that in more cases of hypernephroma than we know about there are extrarenal angiomatous lesions. Maybe there are angiomas in many of our cases, and we never know anything about them because they don't give any symptoms.

Dr. Herman L. Kretschmer (Chicago, Ill.): Dr. Deming has presented a very interesting group of patients, and they once

more demonstrate the fact that the urologist in his work touches upon many fields outside of his own field. The subject of metastatic osteomyelitis of the spine is a very interesting one. I have seen three patients who had metastatic osteomyelitis of the spine. The first patient was a man with a single kidney who was operated on for a stone in the ureter which was removed successfully. Several months prior to the operation for stone in the ureter he had a nephrectomy for a pus kidney. Following the removal of the stone the patient developed a severe pain in the back and ran a low-grade temperature. The physical examination disclosed an interference with function of the spine in that it was impossible for him to flex the spine. A roentgenogram showed the presence of osteomyelitis. This healed with rest in bed.

The second patient was a man who had been operated on four weeks before he came to me. The diagnosis made prior to operation was perirenal abscess. At operation no perirenal abscess was found. The patient complained of pain in the back, a low-grade fever and leukocytosis. He, too, was unable to flex his spine. A roentgenogram disclosed osteomyelitis of the spine. Bed rest and appropriate orthopedic treatment in the form of splints and braces resulted in a complete cure.

The third patient was one who fits in with the patients presented by Dr. Deming, namely—following a prostatectomy the patient developed a metastatic osteomyelitis of the spine.

I am of the opinion that in the patients I just cited the infection was metastatic.

DR. CLYDE L. DEMING (New Haven, Conn.): I would like to thank Dr. Davis and Dr. Kretschmer for discussing my paper. It is gratifying to know that clinics other than mine have had experiences similar to the one described. Apparently these complications have been overlooked in patients with prolonged convalescence and even in some cases which have terminated fatally. There is difficulty in anticipating when such a complication may arise. Greater efforts should be made to prevent and control infections in the prostatic patient. However, the symptoms are so dramatic that we should have little difficulty in suspecting the complication early following any type of prostatic surgery.

(Drs. Cahill, Kretschmer, Paine and Smith had no closing discussion.)

EIGHT-YEAR RESULTS OF CASTRATION FOR PROSTATIC MALIGNANCY

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In 1933 I became interested, for personal reasons, in the reports from foreign clinics of the benefits to be derived from bilateral oöphorectomy in mammary cancer. It is of interest to note that the earliest reference is to Schinzinger,[4] as long ago as 1889, who suggested bilateral oöphorectomy in the treatment of carcinoma of the breast. In 1896 Beatson[2] reported three cases so treated, all for inoperable breast carcinoma. Thompson,[5] in 1902, reported eighty such cases, and noted decided improvement in 22.5 per cent of them. In 1905 Lett,[3] with ninety-nine cases, reported improvement in 36 per cent. They all saw regression of the carcinoma, both primary and secondary lesions, lasting months or even years. Since 1920 roentgen irradiation has been applied rather than oöphorectomy, and the percentage of improvement has been boosted to 73 per cent in Ahlbom's[1] report (1930). The whole subject has been well discussed by Witherspoon[6] in the *Archives of Surgery* in 1936, and brought up to date. By analogy it was easy to assume that perhaps similar results might be accomplished in prostatic carcinoma by castration in the male, and I wish to report results observed by me in five patients in whom castration was performed in our clinics seven, eight and nine years ago, in the hope of influencing inoperable carcinoma of the prostate. We had no methods by which such could or should be measured, and, of course, it was applied only to those cases in which clinical evidences made the diagnosis of carcinoma unquestioned.

Case 1.—George K., aged seventy-two, white, was admitted to the Hospital of the University of Pennsylvania on August 15, 1933, with complete urinary retention. He had experienced increasing urinary difficulty over the past five years, with a sense of incomplete bladder emptying, nocturia as high as twelve times and diuria four times per hour; no hematuria, no pain, but slight burning. He had lost 10 pounds in the past five months.

On examination there was no tenderness over the abdomen, the testicles were normal, and the external sphincter was of normal tone. The prostate was asymmetrical—more enlarged on the right than on

the left—and was hard, fixed, inelastic and nodular. The rectal wall suggested an attachment to the prostate on the right. Pre-operative diagnosis was prostatic carcinoma. Cystoscopic examination showed the bladder to be free of stone, tumor or diverticulum, but there was moderate trabeculation and a large commissural protuberance. The mucosa over the lateral lobes was normal, and there was no cystoscopic evidence of malignancy. A needle biopsy was performed and reported as showing no evidence of malignancy. On August 29, 1933, an operation was performed of bilateral castration and a prostatic resection, and the pathologic report on the prostatic tissue was adenocarcinoma. The patient died in January, 1935, seventeen months postoperatively, at seventy-four years of age.

Case 2.—John B., aged sixty, colored, was admitted to the Germantown Hospital from the Germantown Poorhouse on November 23, 1932, in urinary retention and great distress. He had had increasing difficulty in the past three to four years, had received instruction in self-catheterization, and entered the hospital because of his inability to so relieve himself. A prostatic resection was performed by Dr. Schofield, my assistant, and a pathologic diagnosis of adenocarcinoma of the prostate was made. The patient left the hospital on January 3, 1933, but attended the out-patient department regularly until August 15, 1933, when he was admitted to the ward a second time. On his first admission the prostate was described as "generally enlarged and very firm"; on the second admission as "enlarged, fixed on right and nodular." He was thoroughly studied, and on August 30, 1933, a bilateral orchidectomy was performed, as well as a second transurethral resection. The second pathologic diagnosis on the resected tissue was recorded as "early malignant degeneration." Before discharge six weeks postoperatively the following note was recorded: "Rectal examination shows a prostate of rather normal consistency, fixed on right, with slightly more bulge on left than on right." The patient showed a definite hypertension, and on discharge it was recorded as 225/130.

A follow-up note of four months later (February 16, 1934) recorded a nocturia of two to three times, a good stream and a residual urine of 60 c.c.; also "prostate by rectum feels soft and small in size, much unlike that before his operation."

The third admission was on October 12, 1936—three years and two months after the patient's castration. He had been bedridden for four months, and had experienced increasing urinary difficulty. His prostate was recorded as "enlarged, hard, firm and not tender." Radiographs showed "metastases involving both hips and the pelvis." His third resection, on October 23, 1936, had the following pathologic report: "Marked adenomatous hyperplasia. Cannot make an unequivocal diagnosis of malignancy." A final note states, "This patient seems to have had prostatic hypertrophy with unquestioned carcinomatous areas."

The patient died March 10, 1937, three and one-half years after his castration, at sixty-four and one-half years of age.

Case 3.—William F. S., aged sixty-three, white, was admitted to Chestnut Hill Hospital, August 23, 1933, complaining of progressive weakness, shortness of breath and low abdominal pain. His symptoms were of three months' duration, and questioning revealed that he had a burning sensation on urination, moderate frequency and one attack of severe hematuria. He was transferred to the University Hospital on September 12, 1933, and described as "an emaciated, listless male of sixty-three years, the picture of a wasting disease." Rectal examination presented a prostate "moderately enlarged, left lobe more so than right, and on the left it was nodular, fixed and hard, and painful on pressure." Cystoscopy showed a trabeculated bladder wall and a small diverticulum; the commissure was thickened and elevated, and the left edge of sphincter and superior portions were edematous. Preoperative diagnosis was carcinoma of the prostate.

On September 14, 1933, both testes were removed and a transurethral resection performed. The pathologic report on the tissue study of resected portions of the prostate was benign hypertrophy. Four days after operation, with an elevated temperature, a friction rub over the posterior aspect of the right lung, with râles, and an increased harshness to his previous systolic heart murmur, the patient was transferred to the Medical Service. On this service his prostate was reported "not enlarged but quite hard and elastic and fixed, especially the left lobe which feels finely nodular." A positive blood culture was reported as Streptococcus viridans, which complicated his clinical condition, and death occurred forty-three days postoperatively. An autopsy was performed, and the report did not verify a diagnosis of carcinoma of the prostate. One is left to decide between a typical, clinical diagnostic finding and perhaps the questionable thoroughness of the postmortem study.

Case 4.—Thomas W., aged seventy, white, entered the Hospital of the University of Pennsylvania on December 6, 1934, complaining of frequency of urination and hematuria. For a number of years he had had a nocturia of one to three times, but four months prior to admission he developed a burning sensation on urination, with a dull pain in the lower abdomen. Three months before entering the hospital hematuria occurred and had been intermittent ever since. Hesitancy, a weak stream and dribbling were present. Examination showed an emaciated man of 135 pounds in weight, an asthenic habitus, narrow shoulders and pigeon chest. The left testis was moderately atrophic, though both were small. The left lobe of the prostate was about normal in size, shape and consistency; the right lobe was very greatly enlarged, especially upward so as to form a finger-like projection into the seminal vesicle region; it was hard, irregular, non-tender and definitely fixed. The residual urine was 50 c.c. On December 11, 1934, a

bilateral orchidectomy and a prostatic resection were performed, and the patient was discharged December 18, 1934.

The pathologic diagnosis of the resected tissue was "carcinoma Grade 3 (transitional cell type)." The patient was seen at the Follow-up Clinic on February 9, 1935, when it was stated, "Prostate large, but I believe softer than on previous admission; no tenderness. Says he feels better and voids more easily than heretofore. Has gained weight, though amount unknown. Looks spry. Virility lost. Control good. Residual urine 4 c.c." There is a note from his wife on the history reporting his death on August 8, 1935, eight months post-operatively.

I have reviewed the pathologic sections in these four cases, and have had the diagnoses reconfirmed. It has been especially difficult to trace any record of clinical benefit. The four patients lived seventeen months, three and one-half years, forty-three days, and eight months respectively. Needless to say, we became discouraged, although in two at least there was definite clinical improvement, but this was due probably as much to the prostatic resection as to the castration.

Case 5.—Our one living patient is David L. G., aged sixty-three, white, a private patient of Dr. Schofield, who was admitted to the Germantown Hospital on December 3, 1935, a full year since our last previous case. He complained of urinary frequency, burning and hesitancy during the previous two years, but all symptoms had increased in the past year, and at the time of admission he was voiding every hour, both day and night, and with marked burning. There had been no true pain, but he had noticed marked fatigue. He had been hospitalized previously in Trenton, put on an indwelling catheter, but no relief had been obtained. Physical examination, on admission, showed no important facts, except that the prostate was moderately enlarged, hard, with several palpable nodules. On December 5, 1935, a bilateral orchidectomy and a prostatic resection were performed by Dr. Schofield. The pathologic diagnosis of the resected tissue was adenocarcinoma. The patient was discharged to the care of his referring physician, Dr. A. J. Lettiere, at his home.

This man is alive today at seventy years of age, six and one-half years since his castration. I have been in correspondence with Dr. Lettiere and would like to quote his letter of April 30, 1942: "Patient was in good health, free from pain or urinary difficulty until April, 1941, when he came to me with low back and right hip pain, and the inability to move his right leg. Radiographs revealed massive metastases of dorso-lumbar spine. Three courses of epidural and subdural absolute alcohol injections relieved all pain, with eventual recovery of the function of the right leg. After the use of stilbestrol, and several

courses of x-ray therapy to the prostate, the patient is now free of all pain and voids well enough to dispense with a catheter. The prostate is hard and of relatively normal size. His appetite is good, his weight constant and his general condition good."

CONCLUSIONS

What can we deduce from this small group of cases, now seven, eight and nine years since orchidectomy was done in the hope that it would affect the course of prostatic carcinoma? First of all, it has not cured any. Against this, let us put (secondly) that in three patients it has apparently played a part—how specifically I cannot say—that ameliorated pain, fatigue, lassitude, increased appetite and weight, and life became again worth while. Thirdly, how much of the symptomatic improvement should be credited to transurethral resection? In other words, was the resection partly or entirely responsible for the alleviation of urinary retention and nocturnal frequency? Fourthly, in the one patient who is still alive, six and one-half years since castration—though with x-ray proof of metastases—several accessory therapeutic measures became necessary and were applied, such as spinal absolute alcohol injections for pain, roentgen therapy to the prostate, stilbestrol injections, et cetera; he is reported comfortable. Fifthly, each case was one of advanced carcinosis, and metastases were probably existent at the time of castration. Should we limit the procedure to those in whom we feel sure that metastases are not present? Should all have stilbestrol routinely as a postoperative measure? Our greatest present need is to follow all cases by some biochemical test and by x-ray studies, in the hope of finding a means to evaluate clinical improvement. Surely, "Life is short, and the art long: the occasion fleeting, experience fallacious and judgment difficult."

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CARCINOMA OF THE PROSTATE GLAND TREATED BY CASTRATION

REPORT ON A SERIES OF CASES

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This report of the clinical course in six cases of carcinoma of the prostate gland in which castration was performed is presented in order that it may be added to the many hundreds of reports of cases which will require study before this newer method of treatment can be evaluated accurately. That there is an immediate favorable reaction following castration in most cases is now generally recognized, thanks to the work of Charles Huggins. Yet I clearly remember Dr. Barringer, when I visited his clinic at the Memorial Hospital in the nineteen twenties, presenting a case of carcinoma of the prostate gland in which marked signs of improvement had followed therapeutic castration by roentgen rays. Moreover, Ferguson wrote on May 7, 1934, in a Correspondence Club letter: "I would like to cite, without attempting to offer an explanation, a peculiar phenomenon which has occurred twice in a group of six cases of carcinoma of the prostate with widespread metastases. These six cases were treated by roentgen castration without giving local treatment of any sort. One of these patients with a Grade II carcinoma of the prostate, recurrent within six months after a radical prostatectomy, and with widespread bony metastases, is now alive and feeling perfectly well twenty-four months since roentgen castration. In that period his weight has increased from 180 to 250 pounds. Frequent check-ups of the bony lesions by x-ray show the process to have been entirely arrested but there has been no regression in these lesions." It is regrettable how frequently conservatism delays progress and prolongs man's suffering!

The question naturally arises: How long will such remissions last? Can they be hastened by the additional administration of an estrogenic hormone? Does the gain in weight and the diminution of pain from metastasis indicate a prolongation of the patient's life, or simply that the fatal outcome is approached with less suffering?

My first case would seem to indicate that the duration of the disease is not necessarily shortened but that its progress is associated with less suffering as a result of castration.

REPORTS OF CASES

Case 1.—The patient, aged sixty-six years, had to give up golf in the autumn of 1939 because of pain in his side. His prostate gland was stony hard, but roentgenograms failed to give evidence of metastasis. The quantity of residual urine was 2.5 ounces (75 c.c.). The passage of sounds relieved the patient of his urinary symptoms but the pain in the back persisted. Roentgenologic examination made in January, 1941, revealed characteristic evidence of metastatic new growth in the ribs, spinal column and pelvis.

On June 2, he was given 0.2 mg. of estrogenic hormone, the alpha estradiol dipropionate, three times weekly because he had become bedridden and was suffering greatly from the pain of the metastatic growths. The following day, roentgen therapy was applied to his back and testicles. The relief of symptoms which followed was gratifying and greatly in excess of any observed by his roentgenologist previously. In a short time the patient had gained 10 pounds (4.5 kg.) and was again driving his car. The roentgenologic evidence of metastasis, however, did not recede. In October, after a most satisfactory summer in regard to both pain and voiding, he complained of pain in the neck and there appeared definite evidence of cervical metastasis.

On November 11, 1941, castration was performed. This was followed by the usual remission and freedom from pain, but the patient is now in the hospital again, failing rapidly.

The total duration of the disease does not seem to have been lengthened by more than possibly a few months. The condition certainly never could be said to have been arrested, for the metastatic process continued to progress, as shown by frequent roentgenograms, even when the patient was free of symptoms.

Another clinical question which presents itself is, does the decrease in pain from the metastasis indicate that the metastatic growths are receding? Such recession, of course, is difficult to demonstrate, for the growths are osteoplastic in most cases and it is conceivable that they can diminish in activity and yet present no diminution in their roentgenologic appearance; they may even present an increase roentgenologically. On the other hand, if the metastatic growths are in the lymph nodes such diminution should be demonstrated both roentgenologically and by palpation.

Such diminution occurred in the second case of my series,

wherein the metastatic tumors were in the mediastinum and were at first mistaken for evidence of lymphosarcoma. This patient presented other interesting urologic pathologic features and, as he is known to have been under the care, at different times, of at least five members of this Association, I shall briefly report his urologic history. I shall go into considerable detail because of the association of leukoplakia and carcinoma.

This is the second case which I have observed in which leukoplakia, proved by microscopic examination, has been associated later with carcinoma of the prostate gland. Does the occurrence of carcinoma indicate a carcinogenic tendency of the patient? Certainly the leukoplakia can hardly be explained as precancerous when one considers the histologic characteristics of the ensuing malignant growths.

Case 2.—The man first came under medical observation at the age of thirty-six years at the Tufts Medical School where, in 1902, a diagnosis of right renal tuberculosis was made. Twenty-five years later, in June, 1927, at Pasadena, California, he was examined by Dr. Paul Ferrier, and a calcified right kidney, together with healed pulmonary tuberculosis, was demonstrated. The patient's complaint then was difficult and painful urination with associated rheumatism. In the autumn of that year he went to Rochester, Minnesota, where Dr. Crenshaw confirmed Dr. Ferrier's findings, and, in addition, made a diagnosis of leukoplakia following removal of tissue from the right and posterior wall of the bladder. This surface was covered by a membrane with raised edges; the membrane was sharply circumscribed and apparently was tightly attached. The finding of prostatitis, grade IV, was considered the etiology of destructive arthritis of the hip and was treated accordingly. The leukoplakia, Dr. Braasch advised, should be treated by the method Rovsing had advocated for tuberculous cystitis. He did not feel that the functionless right kidney was a contributing factor in the patient's complaints and advised against its removal. On returning to Pasadena, the patient entered a local sanitarium and his dysuria was treated by an indwelling catheter. No benefit being derived from this treatment, Dr. Arthur Cecil performed nephrectomy in January, 1928. The following May, the patient returned to the Mayo Clinic. The area of leukoplakia was found to be twice as extensive as before, with much more inflammatory reaction about the edges, and was reported as possibly extending into the urethra.

In June, 1928, the fourth member of this Association, Dr. Verne Hunt, destroyed the leukoplakia with a red hot cautery, with the patient under regional anesthesia. The entire surface was seared over, which caused the superficial epithelium to roll up and become readily removable. The patient was dismissed in October. He was free of urinary

symptoms until 1936 when Dr. Ferrier, finding a median bar obstruction, resected the vesical neck. Improvement was so marked that not until 1940 did the patient again seek medical aid because of the return of his former urinary symptoms.

Examination revealed 6 to 8 ounces (180 to 240 c.c.) of residual urine, with no apparent urinary obstruction except the scarred vesical neck. In searching for a possible neurologic explanation for the residual

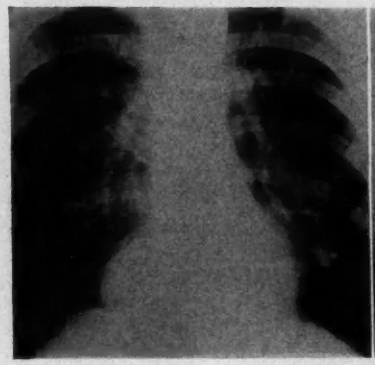

Fig. 1

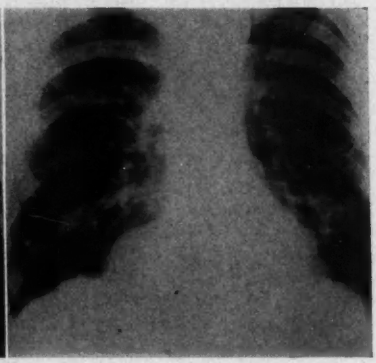

Fig. 2

urine, a large mediastinal tumor was discovered (Fig. 1), and a diagnosis of lymphosarcoma was made. In August and September, 1940, this tumor was exposed to 150 r on six occasions with no appreciable result. During the autumn and winter the patient's urinary difficulties, although considerable and often distressing, did not elicit much professional interest because of his evidently hopeless outlook.

I first saw the man in April, 1941, at which time he had overflow incontinence. The urine was foul smelling but had never been hemorrhagic. He appeared very toxemic. Rectal examination revealed only a scar in the prostatic region. At cystoscopic examination in the office, 10 ounces (300 c.c.) of residual urine was removed; the vesical mucosa was seen to be replaced by scar tissue but there was little evidence of inflammation. After the cystoscope had been removed and a Buerger urethroscope inserted, a tumor was discovered on the dome of the prostatic urethra; it was this which apparently was causing the urinary obstruction. It seemed strange it had never bled as it looked malignant and was thought to be a carcinoma of grade III or IV. The next day, at the hospital, the tumor was resected transurethrally, together with some of the scar tissue about the orifice of the bladder, and the site of the tumor was subjected to thorough electrocoagulation. The pathologist reported adenocarcinoma, grade III, and a diagnosis of

carcinoma of the prostate gland, with mediastinal metastasis was made (Fig. 2).

On July 3, 1941, bilateral orchidectomy was performed. The patient visited the office six months later (Fig. 3). The mediastinal tumor had receded to half its original size and the patient stated he felt well in every respect. His urine was clear, sparkling and microscopically negative. A second roentgenogram taken nine months after operation,

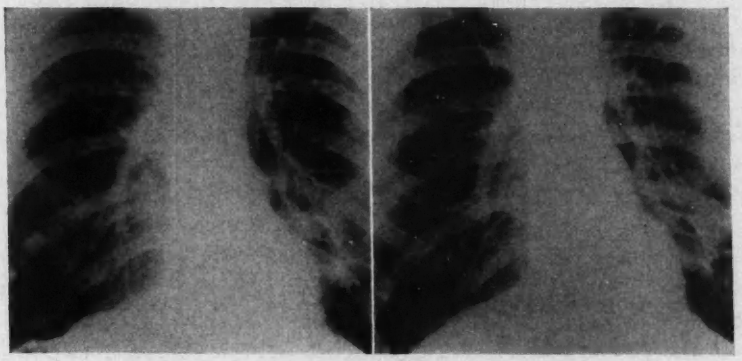

Fig. 3 Fig. 4

showed the tumor to have completely disappeared (Fig. 4). The patient told me he considered himself cured when I stopped at his hotel the day I left Pasadena. I wish I agreed.

My third patient represents the second case I have encountered in which carcinoma of the prostate gland occurred before the age of fifty years. I have wondered if the sudden cessation of the androgen hormones in these younger individuals, whose production normally is presumably plentiful, will not be followed by more rapid improvement and regression of the malignant process than could be expected from the sudden removal of the male hormone from a man who is, say, in the late eighties of life.

Case 3.—The man related that his symptoms had begun at the age of forty-seven years. He came under my care when he was fifty-two. At that time urinary retention was complete. He suffered so acutely from the typical girdle pains of malignant metastasis that, on the way to the office, he was forced to stop in a nearby town and obtain a narcotic from the local physician. The patient could not trust his driving because of the severity of his suffering.

The man was castrated and he has received 3 mg. of stilbestrol daily since then. Nevertheless, he continues to have erections and he reports that his sexual activities have improved as a result of the treatment. His erections are satisfactory and the discharge of seminal fluid and orgasms are normal. Although general improvement and freedom from pain have been rapid and spectacular, the gland has changed little in size but definitely in consistency. Residual urine continues to measure from 200 to 300 c.c.

The persistence of libido and potentia in this third case is still another proof, if such is needed, that the cortical centers are as important in sexual matters as are the glands of internal secretion.

The fact that the fourth patient heads a department in the division of liberal arts at one of the universities situated near Pasadena makes his case of particular interest because of the meticulous care he has shown in reporting his symptoms and progress.

Case 4.—When the man was first interviewed in March, 1941, he was sixty-six years of age and gave a history of urinary difficulty of eight months' duration and loss of 18 pounds (about 8 kg.). Residual urine measured 500 c.c.

On April 4, 7 gm. of tissue were removed from the neck of his bladder and was reported to be characteristic of adenocarcinoma, grade III. Some friends strongly urged him to undergo roentgen therapy at the California Institute of Technology where extensive roentgenologic treatment of carcinoma of the prostate gland has been done. However, inasmuch as he was voiding freely two weeks after resection he decided, on my suggestion, to leave well enough alone.

As he was giving his wife estrogenic hormones hypodermically twice a week, I instructed him to take the same dose, starting May 9, 1941. The gland immediately shrank noticeably in size, the urine became sparklingly clear and he had no residual urine. Tiring of the repeated hypodermic injections of estrogen, he decided to undergo orchidectomy, which was performed August 22, 1941.

On January 5, 1942, he wrote, "May I report in? I am bothered by the way I am gaining weight. I am up to 187 pounds, two above my previous record, and going strong. Soon, I shall have to buy new clothes."

But three months later he wrote, "I wonder if you can suggest something to reduce the continued barrage of heat flashes. I feel miserable as they come up six to ten times a day. I also usually awaken with a backache or hipache—I find it hard to do mental work."

In Case 4 the benefits of the castration would seem to be wearing off approximately six months after the operation, much as they did in Case 2, and I feel that the course of the disease must

be considered to have been made easier, not shorter, by the surgical operation.

Case 5.—The man was seventy-seven years of age. The case is of interest inasmuch as an osteopath had massaged the malignant gland at regular intervals for six weeks before I saw the patient. If metastasis can be induced by vigorous massage he should have had it. The only appreciable result of the massage was loss of 20 pounds (about 9 kg.) and corresponding debility. The gland was typically hard and indurated.

Orchidectomy was performed and, a month thereafter, the gland had so softened that diagnosis by palpation would have been impossible. The patient's physician, from his home town in Oregon, stated on May 11, 1942, that the old gentleman was again attending the Rotary luncheons regularly and was making a fourth hand at bridge every afternoon at the club.

Case 6.—This man was seventy-one years of age. His case is noteworthy chiefly because he gave a history of an earlier cancer of an ear and lip. When first seen by me he was in a state of acute retention with a SBP of 240. Transurethral resection demonstrated carcinoma of the prostate gland. Administration of stilbestrol, 1 mg. daily, was started in December, 1941, and, in one month, the gland had softened as much as the one in case 5 was softened following castration. Two months later, in February, the patient decided to undergo orchidectomy as he was tired of taking the medicine. His course since then has been without incident, the urine is clear and sparkling.

I have been interested to learn if removal of the androgenic hormone in these cases would result in absence of that unknown bactericidal property found in the urine of patients with carcinoma of the prostate gland, which keeps the urine clear and sparkling in so many cases in spite of the presence of considerable quantities of residual urine. To date I have observed no change in this quality as a result of castration.

HISTOPATHOLOGIC STUDIES IN PROSTATIC CARCINOMA UNDER TREATMENT BY CASTRATION, THE INJECTION OF DIETHYLSTILBESTROL OR BOTH

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Since I presented my observations on this subject a year ago, I have learned much of interest, some pleasing and some otherwise. Dr. Charles Huggins' research work and observations on castration, as well as many others and my own, present a most stimulating and encouraging outlook.

Before continuing I wish to correct the statement that "Walter Kearns demonstrated regression with stilbestrol in dog prostates," which I made last May. It was Huggins and Clark who demonstrated these changes.

In 1905 Lett described the results of bilateral oöphorectomy for advanced carcinoma of the breast, eight years after Beatson had advocated it and in which he reviewed ninety-nine case histories. Of the ninety-nine cases only one was considered a five-year cure in spite of the immediate spectacular response such as we are now experiencing following castration for carcinoma of the prostate. Without going deeply into the chemical background it would appear that our ability or inability to maintain low androgen content in the body of the individual who has a cancer of the prostate is going to be the main problem involved in the control of cancer of the prostate. If this is true, then it will mean that we will have to maintain this low androgen status by castration, the administration of estrogen, or of some other similarly acting substances.

The dose of estradiol dipropionate and diethylstilbestrol is a very interesting problem, and much more experience will have to be gained before we will know how to utilize these substances to the best advantage. It seems likely that we shall not utilize uniform dosage for every case, as each one is a separate and distinct problem.

The principal theme of this presentation is concerned with the microscopic study of prostatic malignant tissue after the adminis-

tration of estrogen or castration or both. The microscopic observation in these cases was made by Col. James Ash, U.S.A.M.C. Unfortunately, no one has as yet been able to examine the site of osseous metastatic lesions which have once existed and then com-

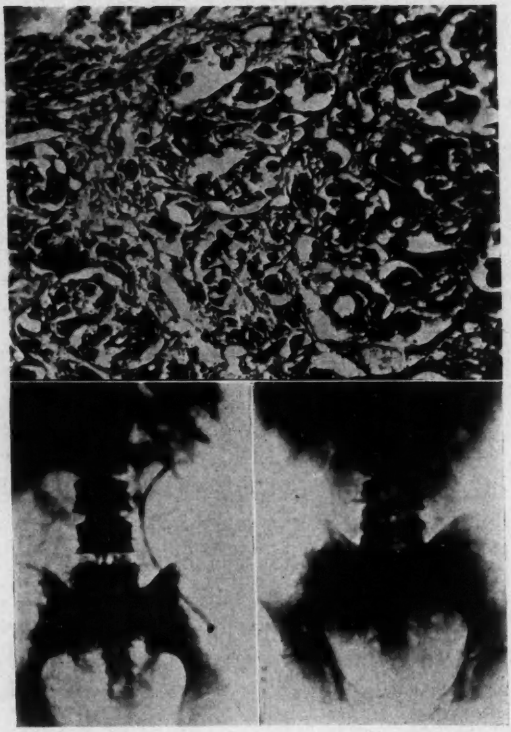

Fig. 1. *(above)* Case 1.

Fig. 2. *(below)* Case 1. The left view was taken after the administration of diethylstilbestrol; that on the right before.

pletely cleared up following castration, in order to determine whether the malignant process still exists in the bone. The closest that we have been able to come to this is one specimen which Colonel Ash has examined.

Case 1.—The first case to be presented is one in which the prostate had an inoperable malignancy involving the prostate bladder, right lower ureter and posterior urethra. This patient was given stilbestrol in the amount of sixteen injections of 1 mgm. each over a period of eighty-nine days. At the end of this time he was so much improved that he and his physician wanted to know whether something radical could not

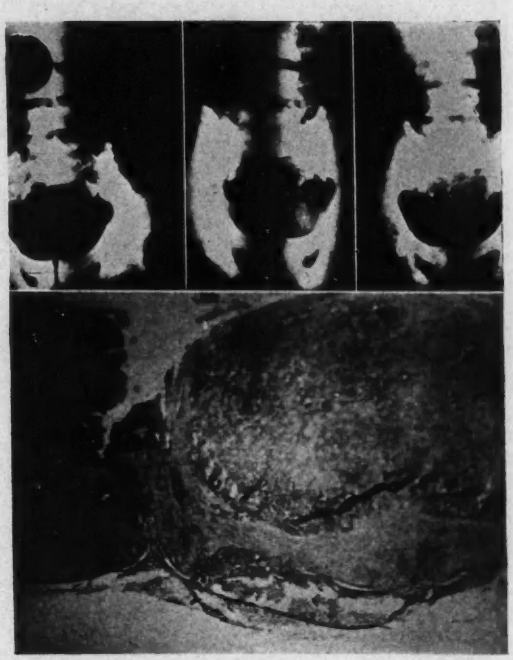

Fig. 3. *(above)* Case 2. The left view was taken before administration of stilbestrol; center, at time of castration; right, four months after castration. This demonstrates no improvement with stilbestrol and improvement following castration.

Fig. 4. *(below)* Case 2. Adrenal area.

be done. A left ureterosigmoidal anastomosis was attempted, but on account of previous peritoneal inflammatory processes the sigmoid could not be mobilized, so a left inguinal ureterostomy was done. Following this the entire bladder, lower right ureter and posterior urethra and prostate were removed in one mass.

Figure 1 shows a nodule on the lateral border of the prostatic mass

which grew rapidly the ten days before surgery. The tragic part of this experience was that a roentgenogram taken during convalescence demonstrated extensive involvement of the spine and pelvis had developed in a period of four months.

Figure 2 represents the only instance where the malignant process

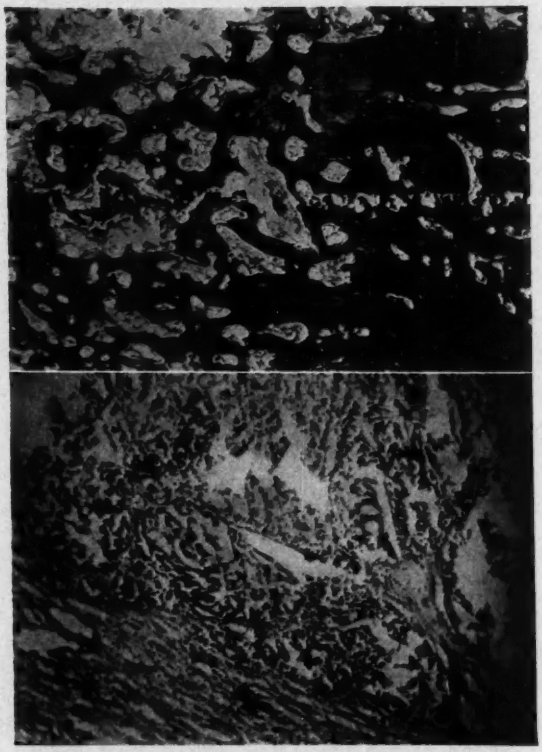

Fig. 5. *(above)* Case 2. Vertebra.
Fig. 6. *(below)* Case 2. Prostatic area.

went through the individual like wild-fire following the administration of an estrogen and this in spite of improvement in the general condition. The histopathologic study, according to Col. Ash, is a typical carcinoma of the prostate with no characteristics which can be interpreted as being due to treatment.

Case 2.—The next study is from an autopsy on a patient who had fifty-four 1 mgm. doses of stilbestrol over a period of five and one-half months, following which a castration was done on June 19, 1941. As a result he got along very nicely. He died on February 15, 1942, of pneumonia eight months after castration (thirteen months after hormonal therapy).

Three roentgenograms are shown (Fig. 3) which demonstrate no

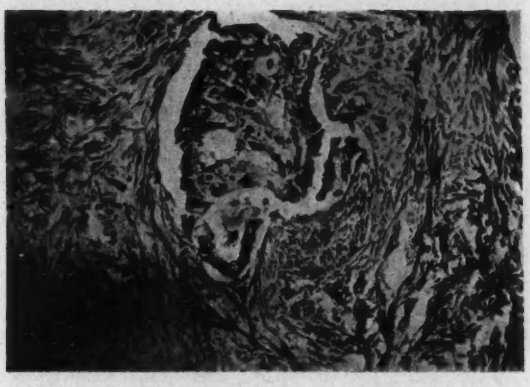

Fig. 7. Case 3. Tissue from the prostate.

appreciable change during stilbestrol injections but what appears to be partial reëstablishment of bony architecture four months after castration. The autopsy demonstrated a metastatic lesion in the right adrenal and the photomicrographs (Figs. 4, 5 and 6) are from the adrenal, vertebra and prostatic area. It was very difficult to recognize any prostate at autopsy as it had almost completely disappeared as a definite entity. Carcinoma cells were present in the region where the prostate was.

Case 3.—The next study is from an individual who had had stilbestrol administered, 2 mgm. a day orally (180 mgm.) plus 1 mgm. hypodermically for sixteen doses over a period of three months. I saw him in consultation and thought that he had a benign hyperplasia of the gland with retention, so I attempted to do a suprapubic prostatectomy. Upon opening the bladder I found that the patient had a malignancy which involved the trigone.

Colonel Ash states that there is nothing in the tissue from the prostate (Fig. 7), from a microscopic standpoint, that is characteristic of anything except typical prostatic carcinoma.

Case 4.—The next tissue is an interesting section of a gynecomastia

which was produced in one patient who had had 45 one mgm. doses of stilbestrol over a period of eight months and the breast was removed at the time of castration, in August, 1941. This patient was castrated because it was felt castration would fulfill his requirements of optimal control better than diethylstilbestrol. It was interesting that a diabetic

Fig. 8. *(above)* Case 4. Breast tissue.
Fig. 9. *(below)* Case 4. Nipple.

condition which required 12 units of protamine zinc insulin a day has not required further insulin up to the present time (nine months). (Figs. 8 and 9.)

The only conclusion that can be drawn from this very small study at this time is that from the microscopic standpoint no

changes occur from a histopathologic standpoint that are characteristic of any modification of carcinoma of the prostate cells, with our present methods of staining. This study suggests the necessity for further interest and experimentation in certain biochemical staining methods in an attempt to bring out changes, if they exist, which can be recognized. The stain of the prostatic epithelial cells as practised by Huggins, utilizing the method of

Fig. 10. Acid phosphate in rich concentration in carcinomatous acini in neoplasm of the prostate. The demonstration of the enzyme in this tissue was made by the method of Gomori.

Gomori (Fig. 10), is interesting and I hope will pave the way for further endeavor involving new staining methods of a similar nature.

We are looking forward with keen anticipation to the time when we will have the opportunity of having a complete histologic examination of tissue from the site of osseous or other metastatic lesions which were present and disappeared from a roentgenological standpoint.

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THE ENDOCRINE TREATMENT OF CANCERS OF THE PROSTATE

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Those who have treated a considerable number of patients with cancers of the prostate have found little encouragement in their results. The disease is important and it has been closely studied. It affects perhaps 5 per cent of all men who reach the age of sixty years and histologic examination of a large number of prostates removed for benign hyperplasia has shown carcinoma in approximately 20 per cent. Intensive efforts have been made to treat the disease successfully. Radical operations have been devised for removing the entire gland with adjacent structures; large doses of external radiation have been applied and radon seeds have been implanted through both perineal and suprapubic approaches. Despite the most careful applications of these forms of treatment the results, in general, have been little more than various degrees of palliation.

Against this background of well deserved pessimism the announcement of Huggins[4] stood out in marked contrast. This investigator reported that after the relatively insignificant operation of castration, patients with advanced prostatic cancers improved in general, their primary tumors became smaller and metastases regressed. White, in 1893,[8] showed that castration of dogs was followed invariably and promptly by atrophy first of the glandular and then of the muscular elements of the prostate. There was coincidental reduction in both the bulk and the weight of this organ. The same writer two years later[9] reported generally favorable clinical results in a group of 111 patients castrated for prostatic enlargement.

In 1898 castration was recommended for the treatment of carcinoma of the breast. Although this never proved highly successful, it seemed to influence a number of investigators to study the effects on prostatic cancers of modifications of the endocrines. In 1935, Kutscher and Wolbergs[6] showed that the prostate gland contained a phosphatase having maximum activity in acid solutions.

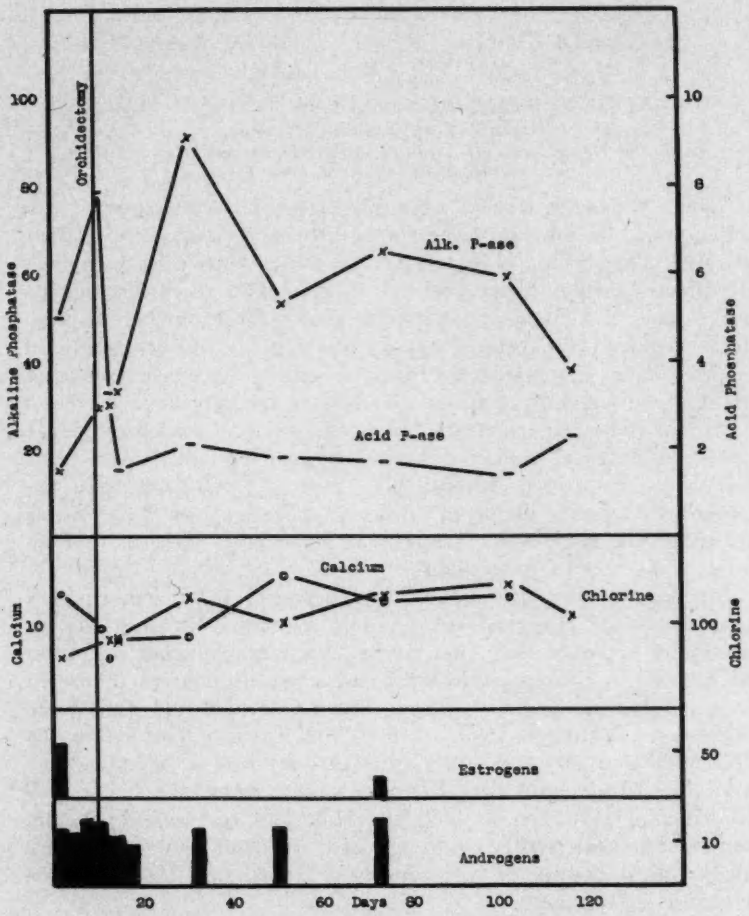

Fig. 1. Acid and alkaline phosphatase in units per 100 c.c. Calcium in mg. per 100 c.c. Chlorine in meq. per liter. Estrogens in mouse units excreted per seventy-two hours. Androgens in mg. excreted per seventy-two hours.

The acid serum phosphatase rose above the initial level on the first post-operative day and then dropped abruptly, but remained above normal throughout the period of observation.

The alkaline serum phosphatase rose rapidly, reaching five times the initial value three weeks after castration, and then exhibited a slow downward trend.

In 1936, the Gutmans and Sproul[2] found that bones, the site of metastases from cancers of the prostate, contained this acid phosphatase as well as the usual alkaline bone phosphatase.

In 1938 the Gutmans[1] established the fact that little acid phosphatase could be found in the prostates of infants, and they showed that the substance increased with puberty and was present in the normal adult prostate, the hyperplastic gland and the cancerous prostate. Gomori later demonstrated through his microphosphatase tests that acid phosphatase was present only in the adult epithelial cells of the gland.

A phosphatase is an enzyme which splits organic phosphorus compounds to give free phosphate ions. Phosphatases differ particularly in the acidity or alkalinity at which they show their maximum activity and accordingly they are known as acid or alkaline phosphatases.

For a number of years we have measured the acid and alkaline serum phosphatases in patients suspected of having prostatic cancers and have learned that these assays not only are accurate diagnostic tests but also show the response to treatment of the disease in soft parts and in bones.

In his ingenious animal experiments Huggins and his coworkers[3,5] isolated dogs' prostates from their bladders and studied the normal excretion of prostatic fluid. He then demonstrated that the administration of androgens stimulated prostatic activity and increased the flow of prostatic fluid. He also found that the administration of estrogens promptly put an end to the flow of

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Fig. 1 (Continued)

During this time the metastatic areas in the bones increased in size, number, and degree of osteoplasia.

The serum protein and inorganic phosphate showed only minor changes and are not shown in the figure.

The serum calcium dropped to abnormally low values immediately after castration and later returned to normal. This is a frequent finding, the significance of which is not yet apparent.

The serum chlorine paralleled the alkaline phosphatase throughout. This parallelism has been observed in several patients and may indicate a relation between the adrenals and alkaline phosphatase.

Estrogen assay was unsatisfactory owing to the toxic effect of the urine of this patient on mice, but there is evidence that estrogen excretion fell after castration.

Androgen excretion showed a transitory fall after castration, and then rose to the initial values.

this substance. He learned that androgens caused hyperplasia of the epithelial cells of the prostate and that in some cases metaplasia became so marked under this treatment that the appearance of the gland simulated cancer. Following treatment with estrogens these glands promptly returned to normal. Huggins also showed that after surgical castration prostatic secretion stopped and metaplasia of the epithelial cells regressed. After much animal experimentation Huggins began to castrate men with advanced metastatic cancers of the prostate. His results have been reported from time to time.

In presenting our own experiences of the past eleven months with the endocrine treatment of sixty patients with carcinomas of the prostate gland, we believe that only general observations are justified. The group is too small for statistical analysis and insufficient time has elapsed for an accurate evaluation of the results of treatment. We have attempted to give our patients full benefit of the experiences of Huggins and at the same time fulfill the obligations of a research institution and learn, if possible, the factors which bring about the clinical changes and the nature of these changes. Therefore, we have carefully studied each patient from the clinical, chemical and endocrinologic viewpoints. In addition to frequent clinical and roentgenologic observations before and after treatment, routine assays have been made at short intervals of the acid and alkaline phosphatases, phosphorus, calcium and chlorides of the blood; of the creatinine, androgens, estrogens, and gonadotropic hormone excretion in the urine, and of the basal metabolism.

In our experience surgical castration almost invariably has given spectacular relief to patients with prostatic cancers. Only two men, observed by us, failed to show improvement by either clinical or laboratory criteria and continued an unchanged downward course to die within two and one-half months after operation. With these exceptions castration has been beneficial. We have not withheld treatment because of advanced disease although many patients seemed near death when first examined. In a number of instances patients had been confined to bed for months because of pain due to metastases and had acquired contractures of the lower limbs. It was surprising to see them learning to walk a few days after orchiectomy. Almost without exception pain disappeared within forty-eight hours; appetites became remarkably

good; body weight increased rapidly; strength returned; and a number of these men resumed their former occupations. One suprapubic mass 10 centimeters in diameter, proved cancerous by aspiration biopsy, completely disappeared in two weeks after orchidectomy. A similar soft part metastasis in the groin regressed with equal rapidity. However, we were able to demonstrate diminution in the size of the primary prostatic tumor in only an occasional case and we usually failed to observe a decrease in the residual urine. Although the residual urine was measured frequently, only a few of our patients were suitable for studying this criterion of improvement because either there was no urinary retention or obstruction had been relieved before endocrine treatment was given. Roentgenograms of the bones were made at trimonthly intervals. When demonstrable, metastases seemed to show uninterrupted development in all but two patients. One, eight months after castration, had apparently complete healing of an extensive secondary lesion of the femur, but at the same time he showed little, if any, regression of metastases in the pelvis. The second patient not only had a striking reduction in the size of his prostatic tumor within six weeks but in the same time he showed evidence of healing in a destructive metastasis of the fourth lumbar vertebra.

A considerable proportion of our castrated patients developed moderate edema of the ankles and a few had hot flushes. After improvement had been maintained for a varying number of months, the majority relapsed. In most instances this was first suspected because of a gradual return of pain.

Histologic study of removed testes in practically all cases showed moderate tubular atrophy with slight to marked interstitial cell hyperplasia. All testes we removed appeared grossly within normal limits.

In addition to the patients surgically castrated a number were treated with stilbestrol administered by mouth. It was impossible for some men to take even small doses of this synthetic sex hormone without experiencing nausea and abdominal cramps, but eight patients were able to tolerate from 2 to 5 milligrams daily for a number of months without apparent difficulty. In these cases there was general improvement as great as that following orchiectomy although possibly the changes were somewhat slower. Under stilbestrol, diminution in the size of the prostatic tumor

appeared to take place regularly and there was a corresponding decrease in the amount of residual urine. The conformation of the bodies of some of these men became feminine. Weight was accumulated especially about the hips. Their breasts enlarged, occasionally became tense and painful, and the nipple and areolae turned dark brown. Measurements showed a decrease in the size of the penis and testes. As yet we have noted no relapses under stilbestrol treatment, though one patient failed to respond favorably. This hormone has proved beneficial when relapses have followed surgical castration but the improvement has appeared less than in those treated primarily with the drug.

It is of interest to attempt to correlate the chemical and endocrinologic changes with the clinical courses of these patients. Figure 1 shows the changes which took place in the acid and alkaline phosphatases, chlorides and calcium of the serum and in the excretion of the estrogens and androgens of a representative patient following orchiectomy. This man had unusually extensive bone metastases. No relapse has been observed in this case over a period of four months.

The prostate gland is the only organ which contains large amounts of acid phosphatase. This enzyme does not enter the circulation from the normal, hyperplastic or cancerous prostate in demonstrable amounts while the capsule of the gland is intact. We know this is true because the normal range of values of both acid and alkaline phosphatase is the same in men and women. When prostatic cancers infiltrate adjacent soft parts, or when they metastasize to distant soft parts or to bones, acid phosphatase usually enters the blood stream and can be measured in the serum. The acid and alkaline phosphatases in the serum of our patients were determined by a modification of the Bodansky method which is described elsewhere.[10] Sodium-β-glycerophosphate was used as substrate throughout. Normal values for acid phosphatase were 0 to 0.7 units per 100 cubic centimeters of serum when the alkaline phosphatase was normal, or as high as 0.9 units per 100 cubic centimeters when the alkaline phosphatase was high. Values above 1.0 unit per 100 cubic centimeters were considered pathognomonic of metastasizing prostatic cancer. Normal values for alkaline phosphatase were 1.5 to 5.0 units per 100 cubic centimeters. While increased acid serum phosphatase indicates an extension of a prostatic cancer, a normal quantity of acid serum phosphatase

occasionally is found in the presence of an extensive tumor. However, while false negative tests may occur, increased acid phosphatase has not been found except with this disease.

In describing the results of our phosphatase assays we have omitted patients on whom we had no adequate readings prior to treatment, those who received radiation at such a time as to influence phosphatase determinations and patients who were lost to observation within a month after treatment was started. With these exceptions we have records of the acid and alkaline phosphatases of the serum before and after surgical castration of twenty-six patients with prostatic cancers.

In nineteen of the twenty-six patients the acid serum phosphatase was elevated before treatment was given. In sixteen of the nineteen the quantity diminished during the two months which followed castration. While it seldom reached normal, the decrease in acid phosphatase usually was striking, amounting in one case to a change of from 115.0 to 1.4 units. In three patients there was no significant change in acid phosphatase after castration. Two of these men failed to show clinical improvement after operation and soon died. In the third only a borderline abnormality in acid phosphatase was present. Seven patients had a normal acid phosphatase before treatment and no remarkable changes could be observed after castration.

In a group of seven patients treated with stilbestrol we found changes in acid serum phosphatase similar to those which followed castration.

In eight castrated patients the fall in acid phosphatase was maintained for three months or more after operation, and during this time they showed clinical improvement. Later, there was clinical evidence of relapse in two and this was associated with a rise in acid phosphatase to above the precastration level.

Our experiences, therefore, confirm Huggins' findings and offer clear-cut evidence that withdrawal of testicular hormones or administration of estrogens, for a time at least, causes a marked reduction of acid serum phosphatase. This may be brought about either by diminishing the production of acid serum phosphatase by the prostatic cancer or by lessening the ease with which this enzyme enters the circulation. In patients in whom acid phosphatase does not enter the circulation neither castration nor administering stilbestrol causes it to do so.

Of the twenty-six patients who were surgically castrated the pre-operative assays of alkaline serum phosphatase were elevated in 12. All but one of these men had definite evidence of bone metastases. In eight of the twelve after castration there was a further rise in alkaline phosphatase at some time during the following two months. In the remaining four patients the alkaline phosphatase either did not change or it decreased.

Fourteen patients had normal pre-operative readings of alkaline phosphatase. Five of these had no evidence of bone metastasis and in two cases bone films were not obtained. The alkaline phosphatase assays of these seven patients has shown no subsequent change as yet. Of the remaining seven patients who had normal pre-operative quantities of alkaline phosphatase four had definite evidence and three questionable evidence of bone metastases. In all but one of these men there was a significant rise in alkaline phosphatase after castration. Conspicuous changes in alkaline phosphatase readings have not been observed in patients treated with stilbestrol but the majority of this group had no bone metastases before their treatment was started.

In the patients who have been observed long enough for roentgenographic changes to have become demonstrable, there usually has been a marked increase in the degree of osteoplasia whenever there has been a rise in the alkaline phosphatase. In some cases this appeared to indicate healing, while in others pre-existing metastatic areas have grown larger and new metastatic areas have appeared. In at least four patients, in whom a fall in alkaline phosphatase has occurred after an initial rise, the fall apparently has been associated with extension of the metastases. We have been able to find no correlation between changes in either estrogen or androgen output and alterations in either of the serum phosphatases.

Considerable evidence has been produced by one of us (H. Q. W.)[11,12] and by others to show that alkaline phosphatase is produced in excess by bone as a defense mechanism. This is a non-specific response and may be the result of deficient supplies of calcium and phosphorus, as in rickets; of loss of calcium and phosphorus, as in hyperparathyroidism; or of injury, as in metastatic disease. When prostatic carcinoma has invaded bone, the activity of the injurious agent (prostatic carcinoma) is reflected in the degree of elevation of the acid phosphatase in the blood.

The activity of the bone defense is indicated by the amount of alkaline phosphatase in the blood.

After castration the activity of the prostatic cancer in bones probably decreases as is shown by the drop in acid phosphatase. We should expect that the alkaline phosphatase, an index of the attempt at bone repair, would also decrease as the need for repair became less urgent and would reach normal, several months later, when repair was well advanced. This has occurred in a few of our patients. As previously indicated, however, in the majority of cases the alkaline phosphatase rises rather than falls in the first two months after castration. Three possible explanations of this reaction may be suggested:

1. There may be no increase in the production of alkaline phosphatase, but instead there may be an increased rate of diffusion of this enzyme into the blood. This is unlikely in view of the close relationship between assays of alkaline serum phosphatase and bone activity. However, certain osteogenic sarcomas contain abundant alkaline phosphatase which does not enter the circulation. Hence, there is the possibility that a shift in hormone balance may cause a change in the diffusibility of phosphatase.

2. The rise in alkaline serum phosphatase may indicate response to increased injury. This is improbable because of the coincidental reduction of pain and decrease in acid phosphatase. However, in some patients metastases have spread in the absence of symptoms and with normal acid phosphatase. Therefore, the possibility of a temporary acceleration of bone injury cannot be dismissed entirely.

3. The shift in hormone balance following castration may stimulate the regenerative capacity of bone. This raises considerations of considerable significance. Many investigators have shown that sex hormones may influence bone development although the mechanism remains obscure. While we have been unable to observe a close relationship between changes in alkaline serum phosphatase and variations of estrogen and androgen excretion it must be remembered that androgen assays measure a number of different 17-ketosteroids which differ in their biologic activity. It is possible that after castration a shift takes place in the relative amounts of these steroid fractions and this may influence the regenerative capacity of bones. Therefore, a definite answer to this problem must await further work on the fractionation of the ketosteroids.

As 17-ketosteroids are produced by the adrenals as well as by the testes we are now studying the blood chlorides of our patients in the attempt to determine whether, after castration, we can detect evidence of compensatory adrenal hyperplasia.

In studying hormonal changes caused by surgical castration or the administration of stilbestrol we have made frequent quantitative tests of the androgens and estrogens. The principal internal secretion of the testes is supposedly the male hormone, testosterone, which is excreted mainly in the urine as androsterone and aetiocholinone. The androgens or 17-ketosteroids are the excretion products of substances formed not only in the testes but in the adrenal glands, and possibly in the ovaries as well. The rate of excretion of these products in the urine is perhaps the most accurate measure of testicular function because urine is the only body substance containing these steroids in sufficient quantity for practical assay. We have employed the Callow test which depends on the fact that the androgens are steroids having the ketonic or oxygen group in the 17 position. Any substance with a steroid nucleus and an oxygen group in this position will give a purple color under proper experimental conditions with meta-di-nitro-benzene. In using the Callow test we are attempting to measure biologic activity by a quantitative chemical analysis of a group of substances which, although chemically similar, may vary considerably in their biologic activity. Since the Callow test is a non-specific color reaction for any ketosteroids having a ketonic group in the 17 position and since many such substances are elaborated by the adrenals, until these substances can be assayed separately in patients before and after castration we cannot say that a post-castration rise in 17-ketosteroids shows an increase in biologically active male sex hormones. It may indicate merely increased adrenal activity. We have now begun the chemical separation and comparison of the 17-ketosteroids in urine.

In measuring the output of estrogens before and after treatment we have relied on the effects of urine extracts on the vaginal smears of castrated female mice because, as yet, there is no chemical test for small amounts of the female sex hormone.

All reports of laboratory and clinical tests, especially those of Huggins, have shown that the administration of androgens stimulated the epithelial cells of the prostate and made patients with prostatic cancers worse, while treatment with estrogens reduced

the activity of the prostatic epithelium and made the condition of patients with prostatic cancers better. Satterthwaite, Hill and Packard[7] measured by the Callow test the output of androgens before and after castration. They found the expected drop in androgens in nine cases out of the ten studied. Their patients who showed the greatest decrease of androgens after castration improved most. The investigators did not study estrogenic excretion rates.

Of fifty-six cases of carcinoma of the prostate studied in the endocrine laboratories of Memorial Hospital, thirty-four were treated by bilateral orchiectomy. Of these, twenty-seven had preoperative determinations of total estrogens and 17-ketosteroids. The estrogens averaged 16.6 mouse units for twenty-four hours and the 17-ketosteroids averaged 6.1 milligrams of androsterone equivalent in twenty-four hours. Since no control group has been studied we do not know whether these quantities are high, low, or average.

Seventeen of this group of twenty-seven patients have been tested for 17-ketosteroid output one month or more after orchiectomy, while sixteen have had both precastration and postcastration assays of their total estrogen excretion. In all patients but one after castration there was a drop of estrogen output from the pre-operative average of 16.6 mouse units to a postoperative average of 8.5 mouse units. The output of 17-ketosteroids of eleven patients rose after castration; in a single case there was no change, and in five they fell. The average change for the entire group was from 6.1 milligrams of androsterone equivalent to 7.1 milligrams. The average rise in the eleven patients who showed a postcastration rise was 2.3 milligrams.

In sixteen patients we have measured the quantity of gonadotropic hormones before and after castration. Of these, eleven have shown definite postcastration rises, while in five the amount of hormone was too little to assay both before and after castration. In no case has there been a definite decrease in the amount of gonadotropic hormone.

Twelve patients were treated with stilbestrol by mouth in doses of from 2 to 5 milligrams daily. In nine men of this group we made assays of the excretion rates of the total estrogens and 17-ketosteroids before treatment was started. At this time the estrogens averaged 18.2 mouse units per twenty-four hours and

the 17-ketosteroids averaged 8.9 milligrams androsterone equivalent per twenty-four hours. These amounts were slightly higher than we found in the group treated by castration probably because we gave stilbestrol to more private patients who were, on the whole, in a better physical condition.

After treatment with stilbestrol the estrogen output rose markedly as would be expected because stilbestrol, or some active metabolic product, was excreted in the urine. In contrast to our findings after surgical castration the output of the 17-ketosteroids fell in every one of nine cases studied over a period of several months to an average of 5.4 milligrams androsterone equivalent.

In six patients gonadotropic hormone assays were made before and after stilbestrol administration. In none of these was the level after treatment high enough to measure, although three had shown measurable quantities before treatment.

On the basis of these results it seems likely that castration of patients with cancers of the prostate causes a fall in estrogen output in almost every case (fifteen out of sixteen). This fall is marked, averaging more than one-half the pre-operative quantity.

Surgical castration of patients with cancers of the prostate usually causes a marked rise in the excretion of gonadotropic hormone (eleven out of sixteen patients), while the administration of stilbestrol, in three cases out of six studied by us, caused a fall. The result in other cases could not be determined because low levels of excretion prevented accurate assay.

These findings suggest that castration liberated the anterior pituitary from testicular control. This is shown not only by increased excretion of gonadotropic hormone but also by increased adrenal stimulation with a consequent rise of 17-ketosteroids, presumably produced by the adrenal. Stilbestrol, on the other hand, suppresses activity of the anterior pituitary gland, and the excretion of gonadotropic hormone falls as do the 17-ketosteroids of adrenal origin. The fact that with both procedures there is marked clinical improvement is puzzling but it suggests that the gonadotropic hormone from the pituitary (follicle stimulating hormone) is not directly concerned.

These explanations of our findings seem to throw doubt on Huggins' hypothesis that prostatic epithelium, cancerous or noncancerous, responds directly to the presence of androgens. Castration seems to result often in an absolute rise in androgens. However,

this may be only an apparent contradiction because the observed rise may be due to an increase in the excretion of inactive 17-ketosteroids. The true situation awaits animal assay for clarification.

COMMENT

From the clinical viewpoint our observations suggest that patients with cancers of the prostate are made more comfortable when treated by surgical castration or by the administration of estrogens, and perhaps they live longer. The majority, however, after a variable period of improvement, relapse and die of the disease. It may be that endocrine treatment exerts different degrees of benefit on different types of prostatic cancers to such a degree as to provide even a cure in an especially fortunate type. It will be remembered that prostatic cancers may vary considerably in their natural history and in their response to other forms of treatment, such as irradiation. Although we have attempted to differentiate clinical types by their response to endocrine treatment we have been unsuccessful, as yet, possibly because we have observed too few patients.

In our limited experience the clinical benefit which follows the oral administration of stilbestrol is as great as that which follows surgical castration.

From the research viewpoint it seems well demonstrated that the natural history of cancers of the prostate may be definitely modified by changes in the endocrines. These changes can be produced by such measures as surgical castration or the administration of estrogens. It is possible that, from this starting point, not only the cure but also the prevention of prostatic cancers can be brought about by the clinician working in collaboration with the biochemist.

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DISCUSSION

DR. EDWARD L. KEYES (New York, N. Y.): Gentlemen, my opinion is no longer worth anything, so I can speak freely.

The physician has, of course, two functions. He is a priest or a god when he is in his office, and he had better not try to be a priest and a god when he comes to medical societies, because we don't take him that seriously. But our godlike thoughts are not always supported by our scientific opinions. The scientific method is only being born. The sense of our own lack of infallibility became generalized during the last century and it is still in its adolescence, hasn't mentally gotten hold of us yet. I, as I retired, lost the scientific sense and retained only my godlike imagination. Hence neither you nor I need now respect my opinions. Yet, curiously enough, the best practitioner of medicine is the imaginative physician. Brinkley was a swell physician, I have no doubt. He must have cured a great many people. How? By making them fall in love with him. Love, according to the poets, of course, is immortal. According to the sons-of-guns, it lasts just so long. (*Laughter*)

But you, too, are imaginative and when hypnotized by some familiar set symbol, I trust neither your opinion nor that of your patients. I await the passage of the love affair between you. It will not last long.

I have no doubt that at the present moment it is impossible for any gentleman in this room to have sound ideas on the subject of castration or stilbestrol for the cure or for the relief, even temporary, of carcinoma of the prostate. As for myself, I suppose it is all poppycock, because I am unable to share your love affair.

On the other hand, the things that were worth showing today, of course, were what Dr. Bumpus showed, the slides of the fellow's chest where the metastasis has actually disappeared. Is that poppycock? I think so. What is the psychic effect of a good doctor on metastasis in the patient's chest? I don't know.

So proceed with your happy love affair. The odds are against you, but perhaps it is true love, after all. (*Applause*)

DR. LOUIS E. SCHMIDT (Chicago, Ill.): I agree more or less with Dr. Keyes. Before most of you gentlemen started to practice

medicine, I remember that the mortality in prostatic surgery was rather high. Even in those days castration was advised and vasectomy was done for any type of prostatic enlargement. In those days we did not differentiate cancer of the prostate from the ordinary enlarged prostate quite as readily as we do now. Unquestionably, there were some favorable results obtained by castration and by vasectomy; but many untoward symptoms accompanied these operative interferences. Frequently, mental conditions followed these procedures. A great many opinions were expressed about what the relationship might be. Modern medicine has cleared up a good many of these problems. Possibly we were on the right track in those days, but we hesitated to continue.

Later came the day when the diagnosis of cancer of the prostate was established definitely but no operative procedure was undertaken.

Patients suffering from cancer of the prostate came to us for relief just the same then as now. Radium and x-ray treatments came into vogue, and, of course, in recent years the resectoscope has unquestionably been of great value in giving this relief. I simply want to state again today that in the course of twenty-five years of the treatment of cancer of the prostate with x-ray that I still have great faith in its effectiveness. I can recall a list of more than 300 patients with cancer of the prostate treated by x-ray. All of them did not get well, but some of them have continued apparently well until their death without any increased symptoms over a long period, many as long as five or ten years. I have known patients to live that long when the original diagnosis was substantiated in the following years by the course of the trouble.

Now, as far as the length of life of the cancer patient is concerned, I have seen in this group, omitting those cases still under observation, patients who have been treated from five to seven years with the x-ray and made more or less comfortable, their general health maintained, and the individual able to continue his vocation. As far as the amount of x-ray treatment is concerned, there are probably a dozen or more who have received anywhere from 35,000 to 40,000 r unit treatments, and I believe one or two more than that. The majority have received from 25,000 to 30,000 r units. Now, that amount of treatment, as you know, has to extend over a long period of time.

Even metastatic complications have been treated with the x-ray with a certain amount of definite improvement.

There is no question about the value of treating some of these people with the x-rays. Lately, I have added stilbestrol, giving it in the doses that have been mentioned today. I think that in some instances stilbestrol in addition to the x-ray treatment has given greater and quicker relief, and what I would consider satisfactory results, without any operative procedure. If in time it can be proven that these estrogens and endocrine products can remove or decrease tumors as the x-ray does, and that they can prolong life to a greater extent than other methods, and when there is proof that these individuals are cured, I will use this exclusively. But I am inclined to believe that, up to the present, sufficient time has not elapsed to show definitely that the individual is going to live free from cancer and die from some other cause. (*Applause*)

Dr. Leon T. Howard (Denver, Colo.): Of course, I think this is the most interesting subject that has been brought before us, because the layman is more interested in it than we are. It was my pleasure to entertain Charlie Huggins when he was in Denver in February at the Rocky Mountain Conference. He stayed at the house, we sat and talked into the wee short hours of the night on this very subject. He is quite naturally a scientist and I was glad to see him elected to this Association. I am sure that Dr. Dean has presented this matter most scientifically before this society, especially in his different conclusions as to why some of these patients respond and some do not. Dr. Huggins was very definite in his opinion that x-ray would not castrate a patient. He showed slide after slide and talked to me about those cases in which the testicles were removed and sections made and he was firmly convinced that the cells of Leydig were not destroyed by x-ray treatments. He was convinced also that those testicles which weighed less than 6 grams apiece on removal indicated the patient would not respond to castration like those patients in whom the testicle weighed 15 to 20 grams apiece. He was convinced that there is a sex hormone that carries on those probably small testicles and suprarenal glands and pituitary which was not affected by castration and that one must use other hormones to inhibit this growth. I think Dr. Dean has

brought those points out in his paper better than I could give them to you secondhand.

Dr. Huggins was of the opinion that the acid phosphatase would not increase unless, as he said, the growth had gone outside the prostatic capsule. Consequently, we are reaching a basis here in a few months when I think this will all be "harmonized" and we will be in agreement with other physicians and be able to tell these patients what is going to happen.

I have one interesting case that I would like to cite. It is too early, as Dr. Schmidt says, for anybody to form an opinion. This patient has been castrated since February and he has had 8 ounces of residual urine. He had a stony hard prostate, and I did not do a resection, because he had a bleeding at the time. I inserted a retention catheter and castrated him first without a resection. That patient, the day I left, had less than an ounce of residual urine, was perfectly normal as far as his nocturia went, with the exception of one time, which he had for the last four or five years. The question is: Are we going to take a certain percentage of these patients, put retention catheters in them and attempt castration before we do a resection and see what happens from that standpoint? Shall we do this rather than break down a capsule that is already confined in the prostate, with the malignancy inside the capsule, and not by our surgery let those cells extend beyond the prostatic capsule which nature is trying its best to protect? I think that is a point we ought to consider and we ought certainly to try this treatment in a few of those cases.

Dr. George R. Livermore (Memphis, Tenn.): I think somebody ought to say something about this subject as it is one of the most interesting that has come before us.

I have had some experience with the administration of stilbestrol. I have not done any castrations, but in the few cases, about ten in number now, in which we have used stilbestrol, we have been giving a larger dose than Bill Herbst. By the way, Bill was the first one to arouse my interest in this subject, at the American Medical Association meeting last year. In regard to dosage, we give one tablet of stilbestrol, 1 mgm. by mouth, t.i.d.; thus the patient gets 3 mgm. per day by mouth, and in addition we give twice a week, an ampoule of 1 mgm. of stilbestrol in oil intramuscularly in the buttock.

I would like to cite one of my cases, a gentleman eighty-two years

of age, who had a carcinoma of the prostate with complete retention and a residual of about 8 ounces, upon whom we did a prostatic resection. His prostate was hard and indurated, particularly in the left lobe where there were several nodules that felt exactly like cartilage and the diagnosis was confirmed by the microscope. This man, after his operation, gave up completely. He remained in bed and would not get up. By the way, I had to do a suprapubic drainage to get him in shape for his resection. His suprapubic wound did not heal. He had pain in his back, so severe morphine had to be given. He refused to eat, became anemic and was in a deplorable condition. When I got home from that meeting, after talking to Bill, I proceeded to give this man stilbestrol and within three days the pain in his back was gone. In a day or two more he was calling for more food, and in two days longer, he was up and about. He has gradually increased in weight, until he has gained 20 pounds. He is absolutely free from pain. He is able to be up and back at work again. His suprapubic wound has healed. He is voiding freely and easily and is perfectly comfortable. I do not say that he is cured, but if we can't do any more than relieve the pain, I think it is worthwhile.

One other point I would like to make is one that Reed Nesbit, who was a roommate of Huggins, I understand, in college, and who has been collaborating with him in this work of castration, has also reported. That is, that when you start on these cases, the prostate is hard, indurated and nodular and in many of them the prostate becomes soft. In this man eighty-two years of age, I defy any of you to examine his prostate per rectum and say that he has a carcinoma, because I have had several urologists examine it and neither they nor I can find any induration in his prostate.

As to the untoward symptoms that some have reported, I have seen no severe symptoms in any of them. Occasionally there is nausea. Another symptom is soreness in the nipples, which some of them complain of, but it is of no consequence. I have asked this old man of eighty-two repeatedly about it and he answers, "Oh, I can feel it sometimes just a little bit, but it isn't bad at all."

DR. GEORGE F. CAHILL (New York, N. Y.): Dr. Randall's paper has been most interesting. He suggests that for elderly people having carcinoma of the prostate, death is inevitable, and he presents evidence to support this statement.

It may be difficult to determine the amount of stilbestrol absorbed when the tablets are enteric coated because they may not dissolve.

Dr. Dean has shown from the Memorial Hospital that the laboratory findings do not always agree with predictions. It has long been known that the adrenal, testes and pituitary have a relationship and on removal of the testes an increase in adrenal function may replace the lost testicular secretion. One thing apparently has been shown and that is that the presence of a high acid phosphatase means usually metastatic prostatic carcinoma.

DR. MONTAGUE L. BOYD (Atlanta, Ga.): I think that Dr. Dean is the only person I have heard who employed "orchiectomy" instead of "orchidectomy." Some years ago either Dr. Morton or Dr. Chetwood called my attention to the fact that you couldn't find "orchidectomy" in the dictionary, and so far I have not found it in any of the dictionaries I have seen. The proper word is, I believe, "orchiectomy."

DR. DAVID M. DAVIS (Philadelphia, Pa.): I would like to venture to discuss one further aspect of this question. We hear a great deal about the changes which occur in the bony metastases and I think it was Bill Herbst who mentioned that unfortunately, even to date, there is extremely little material available from the actual bony metastases of those who undergo treatment, either by castration or stilbestrol. That, I think, is a very great misfortune. If I recall correctly the slide that Bill showed here a moment ago of a metastasis is rather interesting and typical of what happens in the bony metastases of adenocarcinoma of the prostate. It looked to me as though there was a rather definite increase in the bone trabeculation of the sort which would give a picture of condensation in the x-ray, and that in between the bony trabeculæ there was nothing at all but fibrous tissue. That, again, is a very typical finding. There is, I think, little doubt that the person who knows most about such matters, who has made the most thorough, complete and extensive studies of the pathologic changes in prostatic carcinoma, is Rich of Baltimore. He has shown most conclusively that very frequently the metastatic growth within the bone marrow is comparable with that of ringworm. In other words, the active cells advance towards the periphery and very frequently leave in the center of

the original metastasis an area where all of the viable tumor cells have disappeared and have been replaced by fibrous tissue. These fibrotic areas, where viable tumor is no longer present, may be characterized by normal bone trabeculation, by increased bone trabeculation or by decreased bone trabeculation. So regardless of whether you see in the roentgenogram what looks like normal bone marrow, or an area of condensation or an area of rarefaction, it doesn't tell you one blessed thing as to whether there are any active carcinoma cells in that area or not. The only way we shall find out about that point is to study these cases by means of biopsies or at autopsy.

DR. WILLIAM P. HERBST (Washington, D. C.): I would like to say a word, perhaps of a little more optimistic tenor than may be interpreted from some of Dr. Keyes' remarks, in regard to the ultimate result of these observations. It seems to me that with the fundamental biochemical work which naturally holds the key, such as is being done at Memorial and other places, we are bound to find the way in which we can control the proportion of certain of these substances which are in the body. In the meantime, we are going to have to rely upon simple clinical observations.

Now, the dose, I think, is one of the most interesting problems that we are confronted with in regard to the estrogen therapy problem. First of all, let's not forget that estrogens and androgens and all these biochemical substances do have action not only on prostatic cells or breast cells, but they have action on practically every cell in the body to some degree. It is a variation in relativity of effect on all the cells in our bodies that these substances have. So I think we should remember that very definitely, particularly in regard to large dosage of these substances.

Reed Nesbit told me some time ago that they had three cerebral accidents in patients they were treating for benign hyperplasia, giving doses from 1 to 3 mgm. of stilbestrol a day, and he said he didn't believe there was any relationship between the stilbestrol administration and cerebral hemorrhage. Now, it seems to me that there is likely to be a relationship for this reason. I have observed on two patients to whom I have been giving these estrogens, the development of purpuric phenomenon with no corresponding typical blood changes. I have seen a conjunctival hemorrhage occur. Interestingly enough, I gave these patients calcium gluconate by

mouth in order to control those phenomena and I did control them, but I can't give the explanation. There just isn't any so far as I know up to the present time. In view of those observations, it seems to me there is a very definite likelihood that the fibrous tissue cells in blood vessel walls, in the brain, may be influenced by these substances which we are injecting into people or giving them by mouth, which may so change the tensile strength of the walls of those vessels that they will pop. I think that is really a very worthwhile thought to keep in mind, even though we are not able at the present time to prove it to be true.

There is another thing I want to call to your attention in regard to dosage. Dr. Deming and a number of the other men have contributed in the field of effect of estrogenic substances on prostates in animals, and the majority of them have reported increase in size and metaplastic changes in those glands, but if you will go into the dosage, you will find that the doses they have utilized were very large doses. I believe that in the human if we persist and insist on giving these tremendous doses, that we are very likely to produce metaplastic change in the human prostate gland. It seems to me that has very definite bearing on our policy in regard to dosage.

The longest period I have given estrogen to any patient was twenty-two months up to the present time, and so far he has had no untoward reaction outside of this purpuric phenomenon.

DR. LIVERMORE: What dose?

DR. HERBST: One milligram only, and that dose has been varied symptomatically. I think we should not give these people more than they need. I think that if 1 mgm. does them some good, we should not consider that 1000 mgm. is going to cure them. We know from the biologic experimentation that has been done that there is a very definite optimal range and concentration of all these hormonal substances, when we notice the effects of them on tissue culture, for instance. There is an optimal range where they act the best and most effectively. It isn't a question that if a teaspoonful is good, a quart is going to cure them, at all.

Now, I have observed other rather interesting phenomena in regard to breast reactions. Some patients have no breast reaction whatsoever. I have seen unilateral gynecomastia in two instances. There are so many interesting phenomena that we are observing and

we are going to observe, that we just don't know the answer; it must be chemical in the end.

DR. DEAN: I wish to thank the discussers for their kindness. I have nothing further to add.